PRACTICAL ENDOCRINOLOGY

by

HENRY R. HARROWER, M.D.

SECOND EDITION

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Reading is dangerous
because it is so often a
substitute for thinking.

—*Hugh Black, D.D.*

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PREFACE TO THE 1957 REPRINTING

IN EVERY field of knowledge, there are works of certain men that afford the cornerstones for subsequent building.

One of these men is Henry Harrower. His review of the literature and his sage analytical comments withstand the test of time. They give the reader the facts as discovered up to the time of his review. Since we all must absorb such facts in progressive increments, the mere date of 1931 simply means that here we have the foundation for what has since been built. We need the foundation first, and there is so much confusion today in the endocrine concepts and in the use of endocrine products that it is important to get back to fundamental facts. Here Dr. Harrower is a Rock of Gibraltar. He is a genius in separating the wheat from the chaff. Just review his comments on vitamins on page 657 and you will realize how well he covered the available information and recorded the truth. The facts do not change, prejudices and commercial influences do. The pendulum swings both ways in cycles of fashion. Men such as Harrower see through the maze of cross influences, the maze of fads and temporary fancies that characterize all progress, the things less astute minds allow themselves to be beguiled with.

No student of the healing arts can fail to consider this book of Harrower's an indispensible reference work, and of absorbing interest in getting the proper diagnosis of the multiple illnesses of a people who are trying out the mass experiment of starving their endocrine glands by the use of foods depleted of essential minerals and vitamins through processing, refining and the progressive depletion of soils.

ROYAL LEE

September, 1957

PREFACE TO THE SECOND EDITION

THE CORDIAL reception that the profession has given this book has made it necessary to bring out a second edition so soon after the first printing.

The general tenor of the comments regarding the book by those who have been kind enough to write letters of commendation, is that it is sufficiently comprehensive and practical to be of service both as a therapeutic manual and as a work of scientific reference. Although it was the general practitioner whom I had in mind in the writing of this book, I am pleased to hear that a number of medical schools are making it available for students.

Even during the three months that have passed since the book first appeared, medicine has been marching on. As the editor of the *Prescriber* says in his Annual Yearbook of Treatment (*Prescriber*, Jan., 1932, xxvi, p. 1):

"Scarcely a month passes without its record of some advance in the study of the internal secretions. These glands one by one are yielding up their secrets, and empirical organotherapy is gradually giving place to rational endocrinology."

Inasmuch as there have been no outstanding discoveries reported either in the field of laboratory investigation or in clinical observation, no alterations have been made in this edition.

H. R. H.

Glendale, California,
February, 1932.

PREFACE TO THE FIRST EDITION

FOR MORE than twenty years I have devoted most of my time and energy to the study of endocrinology, and it has been one of the most fascinating experiences imaginable. During that time, this important branch of medicine has enjoyed an amazing growth. Step by step it has advanced until at present there is hardly a medical man in the whole world who does not have frequent recourse to some form of organotherapy. It is a perpetual source of astonishment to observe how keen has become the interest in endocrinology.

This great advance reminds me of a visit with Sir William Osler in Norham Gardens, Oxford, in the summer of 1913. Sir William, knowing of my special interest in endocrinology, invited me to lunch and to chat. As he sat near the window looking across his garden to the Oxford University cricket grounds, he made a greater prophecy than he realized. "Harrower,"

he said, "the surgeons have been having their innings during the last ten years or so, and now it is medicine's turn. Mark my words, the internal secretions will be the bat with which the runs are made."

Think of the endocrine "runs" made between 1913 and 1924!

The literature on the internal secretions is now so voluminous that the general practitioner, however great his interest, does not have time to familiarize himself with it in detail. He wants something more compact but equally comprehensive. Intensified appreciation of organotherapy among the rank and file of general practitioners has expressed itself in the wide-spread demand for a library of endocrinology in one volume. PRACTICAL ENDOCRINOLOGY attempts to meet that demand.

The attempt is facilitated by a very complete library. Meticulously recorded and indexed are the facts gleaned by my effort to keep abreast of endocrine progress by personal contact and correspondence with students of endocrinology throughout the world.

No apology is offered for certain peculiarities in this book. Since it is designed for practical use, I have of necessity referred to the products of The Harrower Laboratory,* along with those of other manufacturers—endocrine and otherwise—that are in general use to-day. A certain amount of repetition is unavoidable inasmuch as the book is arranged for reference rather than for cover-to-cover reading. The bibliographic data are intentionally limited, since the practising physician usually has neither the time nor the facilities for extensive study of the literature on a given subject. Yet, those readers who wish to pursue the subject more deeply will find in the Appendix (V) references to numerous books and periodicals on endocrinology, metabolism, and biochemistry.

I gladly acknowledge my obligation to many, especially my immediate associates, for their cooperation in the preparation of the manuscript. I must also express my appreciation to a score or more of colleagues who have read portions of the manuscript and given me useful suggestions and advice. Also I am indebted to Mrs. Mary Irish, of the Barlow Medical Library, Los Angeles, and to Mr. J. Christian Bay, of the John Crerar Library, Chicago, for help with certain most elusive references.

Finally, my thanks are due to tens of thousands of physicians throughout the world whose friendly interest and tangible support during the years have made possible many of the developments in my own special work.

H. R. H.

November, 1931.

*Throughout where my own products are mentioned, the asterisk (*) serves as an indicator.

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PRACTICAL ENDOCRINOLOGY

I

ENDOCRINE FUNDAMENTALS

1. INTRODUCTION

ALL KNOWLEDGE is relative. All advice is subject to the acid test of application before it can be evaluated. Information based on experience is worth more than opinions founded on theory.

One of the great masters in medical research, Claude Bernard, of Paris, to whom we are indebted more than to any other for the current conception of endocrine action, said nearly eighty years ago:

"Ardent desire for knowledge is the one motive attracting and supporting investigators in their efforts; and just this knowledge, really grasped and yet always flying before them, becomes at once their sole torment and their sole happiness. Those who do not know the torment of the unknown cannot have the joy of discovery which is certainly the liveliest that the mind of man can feel. But, by a whim of our nature, the joy of discovery, so sought and hoped for, vanishes as soon as found. It is but a flash whose gleam discovers for us fresh horizons, toward which our insatiate curiosity repairs with still more ardor. Thus, even in science itself, the known loses its attraction, while the unknown is always full of charm."

In the immense literature on the internal secretions, there is information enough, but not all of it has passed through what G. W. Crile terms "the crucible of the clinic."

In the nature of things, much advance in this field has had to be based on laboratory research. However, while the fundamental endocrine studies were carried out by physiologists (chiefly the Frenchmen, Claude Bernard and Brown-Séquard), the most important investigations that followed were clinical. Owing to the absence of definite knowledge, this work was necessarily empirical, but none the less fruitful.

It may be worth while to recall that, in the spring of 1891, an English practitioner, George R. Murray, first treated a patient with thyroid extract. The peculiar changes manifest in her appearance were those that are now known to be characteristic of myxedema. To be sure that the extract was properly prepared, the thyroid gland was removed with sterilized instruments from a freshly killed sheep and conveyed at once in a sterilized bottle to the laboratory, where the glycerin extract was prepared. This was administered at first by hypodermic injection and later by mouth. The patient continued to take liquid thyroid extract until early in 1918, when she substituted the dry extract. In 1919, at the age of seventy-four, she developed dropsy and died.

One of the earliest comprehensive texts on the internal secretions, the classic work of my highly esteemed friend, the late Charles E. de M. Sajous, of Philadelphia, the father of endocrinology in America ("Internal Secretions and Principles of Medicine," First Ed., 2 Vols., Philadelphia, F. A. Davis Co., 1903), was based essentially on practical clinical considerations, for Sajous never ceased being a clinician although he was fully conversant with laboratory investigation and possessed a tremendous familiarity with the literature on the subject.

In all the years that have followed, clinical or empirical organotherapy has been practised (at first, more especially, in France) by many physicians who followed the old-time method of clinical observation established by Hippocrates. It was only when their empirical results could no longer be ignored that physiologists accepted the idea that endocrine physiology, normal and pathological, could be worthy of more than theoretical consideration. Once this truth was accepted, experimental work was undertaken intensively, and progressed with such rapidity that, in the course of less than two decades, active principles of several endocrine glands were isolated and the presence of several others was demonstrated. Indeed, as we shall see (II), it has become possible to produce some of these active principles synthetically. The rapid progress of endocrinology, not only theoretical but peculiarly practical, is one of the marvels of modern medicine.

Unfortunately, research workers resorting to animal experimentation are handicapped when they come to apply their experimental results clinically. This fact is at the bottom of most of the misunderstandings in endocrinology.

The great gulf that lies between the physiologist and the practitioner is difficult to bridge. What can be proved in the laboratory may not apply to the patient; the response of an endocrinectomized animal may be very different from that of a patient whose endocrine disorder has developed

throughout the years and perhaps cannot be diagnosed positively before autopsy. Then, too, a most convincing experience in research may not be duplicated "in the hands of an ordinary doctor," as one writer puts it. The endocrinology of greatest practical value is that which can be understood, appreciated, and applied *in the routine of every-day practice.*

Usually, it is the observation of a curious medical practitioner that stimulates laboratory investigation. The physiologist sets out to show cause, explain why, and discover governing factors. This is a far more logical process than the reverse one wherein the physiologist discovers certain happenings in the animal body, bases upon them a therapeutic procedure, and, ignorant of its human practicability, offers it to the practitioner.

Important information about endocrinology is sometimes hidden away among matter that appears to have no bearing on the subject. M. Y. Dabney, of Birmingham, Alabama, read a paper before the West Virginia State Medical Association on "The Relation of the General Practitioner to the Specialist" (*West Virginia Med. Jour.,* Nov., 1930, xxvi, p. 645), from a section of which, entitled "Endocrinology and Specialists," the following is taken:

"Endocrinology, which is just beginning to emerge from the land of fable, will give us, in a few years, fundamental or systemic methods of treatment of a number of local conditions. The causes of many local manifestations may be shown to lie in endocrine disorders, which cannot be diagnosed or treated by attention to any one part of the body. There has been evolved a technic of discovery in the endocrine field which should considerably stimulate the therapeutics of the future, and this field logically belongs to the province of the general practitioner."

This "technic of discovery" is essentially a clinical development, interesting to the practitioner rather than to the research worker, and it is making all the difference between success and failure in the treatment of many supposedly non-endocrine diseases. Using gastric ulcer as an illustration, Dabney continues:

"If the diagnosis of ulcer is proven, causation of the ulcer is still wholly obscure. Almost any neurologist can offer case reports in which ulcer or perforation of an ulcer seems to have been precipitated by an emotional state such as anxiety or fear. Focal infection has been ascribed as the cause of nearly every type of pathological condition. It has been demonstrated that the frequency of peptic and duodenal ulcer is very high in cats and dogs following total extirpation of the suprarenal glands. Certain abnormalities of the intestinal mucosa are perhaps occasioned by failure of the suprarenals. Resection of the ulcer or other local measures may be, therefore, merely treatment of a symptom, when a more general endocrinopathy should be studied.

"We know that the healing of a fracture is influenced by conditions remote from the site of the injury—syphilis or other infections, low serum calcium or phosphorus, lack of vitamin *D*, probably parathyroid dysfunction—conditions not always close to the thoughts of the man highly skilled in bone operations. Similarly, urinary calculus, one of the most ancient of diseases, or calcium and phosphatic deposits elsewhere in the tissues, should be related to the dietary intake of vitamins *A* and *D*, and to the parathyroid glands. Dental caries is shown to be in a large measure preventable. Thus the trend of medical investigation continually indicates the inadequacy, the palliative nature, of a large number of local measures of treatment."

Thus, what once was considered fable is broadening our conceptions of every phase of medicine. I think it may be said fairly that, as our knowledge of the glands of internal secretion increases, the urge to study more and to delve deeper, leads many an interested physician to a standard of medical study and treatment far beyond that with which he was satisfied in years gone by. As Dabney says still further:

"The present knowledge of the endocrines, which is still very small, reemphasizes the need of study of the whole patient before treating any of his symptoms. How difficult it is, then, for these wholly interdependent parts of the body to be apportioned among physicians! The physician of the future should consider each local symptom as a possible manifestation of a systemic disorder, no matter how highly specialized his field may be."

The text-book physician, whose interest in the internal secretions is limited to the actual endocrine diseases—Addison's disease, myxedema, cretinism, hyperthyroidism, gigantism, acromegaly, the Fröhlich syndrome, etc.—is missing the most important part, for how many cases of Addison's disease or hypopituitarism does the average physician meet in a year's busy practice? On the other hand, it is surprising how many times an endocrine factor will complicate an acute infectious disease or a chronic toxemia.

The criticism that the student of endocrinology "sees glands in every case" is a challenge that I have accepted and used to confirm the very fundamentals of clinical endocrinology. *There are indeed glands in every case!* Further, the vital character of the endocrine responses and the extent of their control of the most important of all the functions of the body—circulation, tonicity, nutrition, growth, development, detoxication—place them in the forefront of the attackable features of the problems that are met every day. Therefore I shall stress particularly these features which enter into the daily experience of the practising physician.

2. A BRIEF HISTORY OF ENDOCRINOLOGY

ABOUT THE only way to prepare a truly brief epitome of the history of endocrinology is to submit the available information in chronological form. So the following endocrine chronology has been prepared as a reminder of the mile-stones that mark the way by which we have reached our present position. Some of these markers are not too well remembered, and some of the names upon them are not familiar, yet this record has been carefully prepared and is submitted as a record of achievement unexcelled in any other branch of medicine.

Of course, there are some omissions and, too, credit may not always be accurately given, for it happens that in endocrine research the real work is often done by those who failed to consummate it, and the credit goes to those who later completed it, as in the case of insulin, where the idea of Banting was superimposed upon years of effort by workers scattered over the whole world.

[NOTE: The reader will find it possible to follow developments in a certain field by using the subject index of dates immediately following the main chronological list.]

CHRONOLOGY

B.C.		
1800	1	Organotherapy mentioned in the Hindustan Ayurveda.
1700	14	Kawa-Soutra, a decoction of bucks' testes in milk, recorded in Sanskrit writings as a strength-giving means.
1500	1	Chinese, Egyptian, Greek, and Roman medicine include practices and beliefs that recognize the internal secretions.
500	11	Powdered placenta used as a postpartum remedy by the Chinese.
460	1	*Hippocrates* considers many diseases as a result of various "humours," and uses corresponding healthy organs of animals for relief. He teaches that "it is to the efforts of nature that the attentive and able physician looks for guidance."
400	14	The treatment of impotence with testicular tissue mentioned in the Ayurvedic writings of *Susruta.*
A.D.		
20	1	*Celsus,* a Roman medical writer, recommends healthy animal organs for relief of diseases of corresponding organs in man.
60	1	*Dioscorides,* an army surgeon in the service of Nero and originator of materia medica, advises use of healthy animal organs for relief of disease of corresponding organs in man.
70	16	*Pliny,* in his "Historia Naturalis," says: "Only men and swine are subject to swellings in the throat, which are mostly caused by the noxious quality of the water they drink."

70	14	*Pliny* prescribes testes of donkeys and of stags as aphrodisiacs.
200	1	*Galen* believes cause of disease is faulty mixture or proportion of four body juices—gall, phlegm, blood, and pancreatic juice. He describes the thyroid.
500	16	*Aetius,* court physician at Byzantium, gives first recorded description of goitre.
900	16	Chinese medical writings contain references to medicinal value of the thyroid, and to its use in what is now called myxedema.
1180	16	Iodine (in the form of sponges and seaweeds) for treatment of goitre, taught by the Salernitan surgeon, *Roger,* of Palermo.
1530	16	Endemic nature of goitre in the Salzburg region, and its local coexistence with cretinism, mentioned by *Paracelsus,* of Switzerland. He believes it is caused by metallic and mineral constituents in the water.
1543	10	The pituitary gland named by *Vesalius,* the Belgian anatomist, who believed it was the source of pituita, or the nasal mucous discharge.
1543	16	The thyroid also described quite completely by *Vesalius.*
1552	16	The thyroid described by *Eustachius,* the Italian anatomist.
1563	2	The adrenals described by *Eustachius.*
1573	6	The corpus luteum of the ovary described by *Volcherus-Coiter.*
1614	15	Autopsy of a five-months-old infant, suffocated by an enlarged thymus, published by *Felix Plater,* Swiss physician.
1628	2	The adrenals named "supra-renals" by *Riolanus,* of France.
1656	16	The thyroid described and so named by *Thomas Wharton,* of England.
1705	10	Epileptiform seizures associated with pituitary disease in France by *Raymond Vieussens* (case of Cardinal de Bonsy).
1761	10	Amenorrhea first associated with pituitary disease by *de Haen.*
1762	14	*John Hunter,* of London, transplants testes into fowls, noting effects on secondary sex characteristics.
1772	10	Acromegaly described by *Saucerotte* in France.
1773	1	*C. F. Wolff,* of Berlin, says: "Each single organ of the body, in respect of its nutrition, stands to the whole body in the relation of an excreting organ."

1776 1 *Théophile de Bordeu,* distinguished French practitioner, publishes his doctrine that each gland and organ produces a specific substance which is passed into the blood, and that these secretions are necessary to the organism, thus elaborating Galen's theory.

1776 6 Effects of testicular and ovarian secretions upon the organism observed by *Théophile de Bordeu,* who describes secondary sexual changes in eunuchs and capons as well as in spayed females.

1776 10 *Théophile de Bordeu* conjectures as to the passage of the secretions of the pituitary into the circulation.

1778 10 The pituitary described and named "hypophysis cerebri" by *S. T. Sömmerring,* Prussian anatomist.

1781 10 In *C. Greding's* book (published in Latin, in Leipzig) are reported anatomical changes in the pituitary in epilepsy.

1783 10 *John Hunter* goes to considerable trouble to obtain the skeleton of the Irish giant for study.

1786 16 Exophthalmic goitre described by *C. H. Parry,* of Bath, England.

1789 16 *Malacarne,* of Turin, Italy, publishes a treatise on endemic goitre occurring in the valley of Aosta.

1801 1 *Legallois,* French physiologist, surmises that the diversity of venous blood is acquired because of loss of some substance to the organ through which it passes.

1802 16 An account of "bronchocele" published by *Flajani,* of Italy, in which he connects goitre with cardiac palpitation.

1815 8 Some of the clinical phenomena of tetany recognized by *J. Clarke,* English physician.

1825 16 A posthumous account published of eight cases of exophthalmic goitre, collected by *Parry,* of Bath, from 1786 to 1815. He gives first classical account of the disease.

1829 16 The Swiss physician, *Coindet,* of Geneva, first uses iodine in the treatment of goitre.

1830 15 Thymus death in infants described by *J. H. Kopp,* German physician.

1835 16 Classical description of exophthalmic goitre published by *Robert Graves,* Dublin clinician, in which he notes exophthalmos and palpitation of heart.

1838 10 *M. H. Rathke,* German anatomist, initiates scientific study of pituitary by describing its development.

1838 15 Status lymphaticus described by *Richard Bright,* of Bristol, England, in his work at Guy's Hospital.

1838 16 *J. Inglis,* of Harrogate, England, suggests that iodine in the water supply protects users from goitre (bronchocele).

1840 10 Autopsy performed on an obese woman by *Bernard Mohr,* of Würtzburg: discovery of a tumor-like degeneration of the pituitary gland.

1840 16 Complete description of exophthalmic goitre published by *C. A. Basedow,* of Merseburg. Germans consider it classical, calling the three cardinal symptoms "the Merseburg triad."

1843 1 *Claude Bernard,* French physiologist, discovers that cane-sugar is converted into dextrose in the stomach. (This led to a line of reasoning that revolutionized the physiology of nutrition and metabolism and brought about a new concept of the internal secretions.)

1844 1 *Johannes Müller,* German physiologist, of Coblenz, shows that the blood receives secretions from ductless glands.

1848 4 Experimental work of *Claude Bernard* shows that the liver manufactures sugar, and that this function is in the nature of an internal secretion.

1849 2 A diseased condition of adrenals in three cases of pernicious anemia noted by *Thomas Addison,* senior physician at Guy's Hospital, London.

1849 14 Experiments in transplanting and grafting cocks' testes, by *A. A. Berthold,* of Göttingen, show that they supply an internal secretion: severing the nerves to the gonads does not destroy the sex impulse.

1850 14 *Franz von Leydig,* German anatomist, notices strands of epithelium-like cells in the intertubular connective tissue of testicle, later known as interstitial cells of Leydig.

1850 16 *T. B. Curling,* English surgeon, observes that absence of the thyroid is accompanied by "symmetrical swellings of fat tissue at the sides of the neck, connected with defective cerebral development."

1851 8 *R. Remak,* German anatomist, observes and briefly describes the parathyroids.

1852 1 *W. B. Carpenter,* leading physiologist of England, suggests that ductless glands take from the blood certain products which they restore to it "apparently in a state of more complete adaptiveness to the wants of the nutritive function."

1855 2 A monograph on disease of the adrenals published by *Thomas Addison,* describing eleven cases of "Addison's disease." He suggests that adrenals, as well as thyroid, thymus, and spleen "in some way or other minister to the elaboration of the blood."

1855 2 *Charles-Edouard Brown-Séquard,* in Paris, demonstrates that adrenal ablation is incompatible with life.

1855 4 *Claude Bernard* gives expression to the doctrine of the internal secretions, using the term "internal secretions" in describing the glycogenic function of the liver.

1855 15 *J. H. Kopp* mentions the occurrence of sudden death in childhood following cyanosis and stridor.

1856 2 *Brown-Séquard* finds adrenalectomy invariably fatal in animals.

1856 2 *E. F. A. Vulpian,* French physician, shows that a principle from the adrenal medulla, named "adrenal chromogen," is found in adrenal veins.

1856 16 Fatal results following thyroidectomy in dogs produced by *Moritz Schiff,* of Frankfort-on-Main. (Results were forgotten for twenty-five years.)

1856 16 *A. Chatin,* of France, advances theory that goitre results from inadequate iodine in food and water.

1857 4 A glycogenic substance produced from the liver by *Claude Bernard.*

1860 1 *Liègeois,* of Paris, in his thesis states that the chief function of vascular glands is pouring into circulation materials that change microscopic and chemical constitution of blood.

1864 8 *Rudolf Virchow,* most famous of German pathologists, observes and briefly describes the parathyroids.

1864 10 A lesion in the pituitary body in acromegaly noted by *Verga,* Italian anatomist.

1868 1 *Charles Darwin,* British scientist, states that gemmules are carried from all parts of the body to the ovum to ensure their reproduction.

1869 3 *Brown-Séquard* suggests that the kidneys also produce a true internal secretion.

1872 6 On August 27, *Robert Battey,* of Georgia, removes the normal ovaries from a woman for the relief of a neurotic condition.

1873 16 Myxedema described by *Sir William Gull,* of Colchester, England. (This condition was named in 1877.)

1877 7 *E. Lancereaux,* of Paris, reports profound studies of diabetes in its relation to pancreatic lesions.

1877 10 Pituitary lesion in acromegaly noted by *V. Brigidi,* of Florence, Italy.

1877 16 Myxedema so named by *W. M. Ord,* of London.

1878 16 First therapeutic excision of the thyroid made by the Swiss surgeon, *Theodor Kocher.*

1880 8 The two external parathyroids discovered and described by *Ivar Sandström,* Swedish anatomist.

1881 1 *Paul Bert,* French zoologist, among the first to use the term "internal secretions," referring to "products of secretion which empty into the blood."

1882 16 *Theodor Kocher* reports that thirty out of one hundred thyroidectomies are followed by cachexia strumipriva.

1883 16 *J. L. Reverdin,* of Geneva, proves that the cachexia strumipriva following thyroidectomy is a result of absence of the thyroid function.

1884 10 A pituitary lesion and an enlarged thymus in acromegaly noted by *Edwin Klebs,* of Königsburg, Prussia, in autopsy of a case furnished him by *Fritsche,* of Glarus, Switzerland.

1884 16 Results of sixty fatal thyroidectomies in dogs published by *M. Schiff.* He could prevent symptoms by thyroid grafts, by injections of thyroid juice, or by feeding raw thyroid.

1884 16 Experimental myxedema produced in monkeys by thyroidectomy, by *Sir Victor Horsley,* of London.

1886 7 Experimental diabetes, by the ingestion of phlorizin, produced by *J. von Mering,* of Cologne.

1886 10 Acromegaly so named by *Pierre Marie,* famous Paris neurologist, and connected with disease of the pituitary.

1886 16 Exophthalmic goitre attributed to hypersecretion of thyroid by the German neurologist, *P. J. Möbius,* of Leipzig. Describes related symptom-groups which he believes are caused by quantitative or qualitative alterations in the thyroid secretion.

1888 16 *N. Rogowitsch,* in Germany, discovers that, in myxedema, the pituitary—the pars anteria and intermedia particularly—enlarges after thyroidectomy.

1889 7 Experimental diabetes, by pancreatectomy obtained by *J. von Mering,* of Cologne, and *Oscar Minkowski,* of Alexoten, Russia.

1889 7 Experimental diabetes by pancreatectomy also obtained by *R. Lépine,* of Lyons, France, who offers a "new theory of diabetes," and is first to write words, "pancreatic internal secretion."

1889 14 At a meeting of the Société de Biologie, Paris, *Brown-Séquard,* now seventy-two years of age, in proof of his theory of internal secretions, describes experiments which he carried out in his own person by the subcutaneous injection of testicular extracts. (June 1, 1889, is the date upon which the doctrine of the internal secretions may be said to have been born. *Brown-Séquard* administered testicular extracts to himself, subcutaneously, with benefit.)

1889 15 *Basch, Klose, Matti,* and *Paultauf's* work in Europe with the thymus, throws light upon *status thymicolymphaticus* and certain functions of this gland.

1890 8 Experiments conducted by *E. Gley,* French physiologist, show that tetany is developed by herbivorous animals if parathyroids, as well as thyroid, are removed.

1890 16 *Sir Victor Horsley* suggests thyroid grafting in treatment of myxedema.

1890 16 *George R. Murray,* of Newcastle-on-Tyne, prepares glycerin extract of thyroid and injects same in cases of myxedema.

1890 16 *G. Vassale,* of Italy, successfully injects thyroid extract into thyroidectomized dogs.

1891 1 As a result of his experiments with testicular and pituitary extracts, *Brown-Séquard* formulates a statement of the old Bordeu theory of internal secretions. (Uses pituitary extract for diseases of that organ.)

1891 7 *E. Gley,* of Collège de France, Paris, outlines developments following experimental removal of pancreas.

1891 14 *A. von Poehl,* of St. Petersburg, isolates a crystalline base from semen which he names *sperminum.*

1892 3 *Brown-Séquard* and *d'Arsonval* use renal extract to postpone uremia in nephrectomized animals.

1892 8 Successful transplantation of parathyroids to abdominal wall of a cat made by *A. von Eiselsberg,* of Vienna. Tetany follows removal of graft.

1892 10 Fatal excisions of pituitary in animals made by *G. Marinesco,* of Bucharest.

1893 3 Kidney extract used hypodermically with success in uremia with dyspnea, etc., by *Dieulafoy,* of Paris.

1893 7 *E. G. Laguesse,* of France, suggests that the islands of Langerhans have an endocrine function.

1893 16 *F. Müller,* of Augsburg, discovers high metabolism in cases of exophthalmic goitre.

1894 2 *G. Oliver* and *Sir E. S. Schafer,* of Edinburgh, discover that intravenous injection of adrenal extract causes a rise of blood-pressure and a slowing of heart; also find that certain organic extracts increase blood-pressure, while others have opposite effects—forming basis for classifying internal secretory organs as hypertensive or hypotensive.

1894 10 Fatal excision of pituitary in animals made by *G. Vassale* and *E. Secchi,* of Italy.

1895 2 *G. Oliver* and *Sir E. S. Schafer* concentrate an extract of the adrenal medulla and demonstrate its potency.

1895 2 *N. Cybulski,* of Vienna, reports the cardiovascular action of adrenal extract.

1895 5 *Mironoff,* of St. Petersburg, shows that, after all nerves of a goat's mammæ are severed, the breasts enlarge during pregnancy.

1895 7 *Sir E. S. Schafer* originates idea that human diabetes is caused by deficiency of secretion of islets of Langerhans.

1895 8 Anatomical and physiological independence of parathyroids proved by *A. Kohn,* of Germany, who calls them "epithelial bodies."

1895 10 *G. Oliver* and *Sir E. S. Schafer* find that the mammalian pituitary contains an active principle which, when injected, increases the force of the heart-beat and elevates the blood-pressure.

1895 10 The same Edinburgh workers discover the pressor effect of pituitary extracts.

1895 14 *Griffiths,* of England, describes patients with hypoplastic sex organs whose body configurations resemble those of eunuchs.

1895 16 *A. Magnus-Levy,* of Berlin, discovers the influence of the thyroid upon metabolism, finding abnormally high oxygen consumption in exophthalmic goitre.

1895 16 Iodine in organic combination—iodothyrin—found in the thyroid colloid material by the German physiological chemist, *E. Baumann.*

1896 2 *Szymonowicz* and *Cybulski,* Polish physiologists, working without knowledge of Oliver and Schafer's studies with the adrenals, observe many of the same phenomena.

1896 2 Epinephrine, the chromaffin substance, isolated by *L. Fraenkel,* of Breslau.

1896 6 The first serious attempts at ovarian therapy made at the Landau clinic in Berlin, the preparation being fresh ovarian substance from cow or sow.

1896 8 *Rouxeau,* of France, proves that tetany follows extirpation of all the parathyroids but no signs follow removal of thyroid alone. Confirmed shortly after by *G. Vassale* and *F. Generali,* of Milan.

1897 5 *M. W. H. Ribbert,* German pathologist, transplants mammary tissue under skin of guinea-pigs. Transplants develop and even secrete when animals become pregnant.

1897 8 Removal of parathyroids produces tetany in experiments of *E. Gley.* Thyroidectomy unattended by signs. Mentions large iodine content of parathyroids.

1897 16 *A. Magnus-Levy* shows reduced heat production in patients with myxedema, and gradual raising of oxidative processes during thyroid therapy.

1898 2 Epinephrine isolated by *J. J. Abel,* of Cleveland, Ohio.

1898 2 *Emile Sergent,* of Paris, first emphasizes necessity for supporting adrenals depleted by toxemias or infections.

1898 9 A teratoma of pineal discovered by *L. Heubner,* German pediatrist, originator of caloric feeding, in autopsy of a case of precocious sexual and somatic development in a boy of 4½ years.

1898 10 An extract of posterior pituitary shown by *W. H. Howell,* of Johns Hopkins, to elevate blood-pressure and increase force of heart-beat.

1898 11 Use of sheep's placenta in tablet form as galactagogue reported by *H. Iscovesco,* of Paris. He uses it in more than 100 cases with excellent results. Later he finds it of value in modifying uterine subinvolution.

1899 6 Corpus luteum used by *J. A. Lebreton,* of Paris, for vomiting and other toxic symptoms of pregnancy, with fair results.

1899 6 *J. H. Glass,* of New York, shows that grafting or transplantation of ovaries in ovariectomized women will reestablish menstruation, sexual desire, and general well-being. [Confirmed by *Morris* (1901) also by *Marshall* and *Jolly* (1905).]

1899 6 *A. Loewy* and *P. F. Richter,* of Germany, find that castration diminishes respiratory exchange in both sexes, but that it may be enhanced again by both forms of gonad therapy.

1900 2 *Swale Vincent,* of London, points out that the adrenal medulla secretes into the blood an active substance that produces beneficial effects upon muscular tissue.

1901 2 The first stable and available endocrine active principle, the hormone of the adrenal medulla, isolated by *Jokichi Takamine* and *T. B. Aldrich,* of Detroit, who worked independently.

1901 7 *E. Gley* produces diabetes by obstructing circulation of pancreas by tying its veins.

1901 7 In cases of diabetes in man, degenerative changes in pancreas, especially of islets of Langerhans, noted by *E. L. Opie,* of St. Louis; also by *L. W. Ssobolew,* of St. Petersburg, and *A. Weichselbaum* and *E. Stangl,* of Germany.

1901 7 *L. Popielski,* of St. Petersburg, observes that introduction of dilute HCl into duodenum causes flow of pancreatic juice.

1901 10 Pituitary tumor, with obesity and sexual infantilism, observed by *A. Fröhlich,* of Vienna. Later named *dystrophia adiposogenitalis* by *Bartels.*

1901 16 *Artur Biedl,* of Vienna, urges that parathyroids be left intact in surgical treatment of goitre; also that a portion of thyroid should be spared. [Confirmed by *Jeandelize* (1903), *Walbaum* (1903), *Pineles* (1904), *Erdheim* (1906), and others.]

1902 1 *E. H. Starling* and *W. M. Bayliss,* of University College, London, call secretin, from the duodenal walls, "the pancreatic hormone" because of its homostimulating effect upon pancreatic digestive efficiency; they advance theory that control of body is effected by means of hormones, or chemical messengers, which pass from various organs and ductless glands, via blood stream, to other parts of body, producing biochemical effects there.

1902 7 Degenerative changes in the islets of Langerhans noted in human diabetes by *M. B. Schmidt,* of Germany.

1902 15 *Foulerton,* of Middlesex Hospital, London, first to use thymus extract in treatment of carcinoma. He believes it has an inhibitory action on malignant growths.

1903 1 *C. E. de M. Sajous,* of Philadelphia, publishes the first comprehensive treatise on "The Internal Secretions and the Principles of Medicine" (Philadelphia, F. A. Davis Co.).

1903 2 *Sajous* connects sarcoma and carcinoma with adrenal insufficiency.

1903 6 Experiments of *L. Fraenkel,* of Breslau, Germany, with rabbits, show that the corpus luteum maintains first half of pregnancy.

1903 16 *Arnold Lorand,* of Carlsbad, finds atrophy of thyroid in all cases of malignant growths and suggests thyroid extract as routine for all cancer patients.

1904 2 *Fr. Stolz,* German biochemist, synthesizes a product known as suprarenin, "synthetic adrenalin."

1904 6 *Curtis F. Burnam,* of Baltimore, develops lutein from the corpus luteum of the sow.

1904 15 *D. Noël Paton,* of Glasgow, finds that thymectomy increases the growth of the testes.

1905 4 *A. Gilbert* and *P. Carnot,* of Paris, demonstrate presence of an hepatic principle that exerts a valuable influence upon cholin regulation by liver.

1905 5 Mammary hormone demonstrated by *J. E. Lane-Claypon* and *E. H. Starling,* of London.

1905 8 *G. Vassale,* of Milan, prepares a substance from the parathyroids which he calls "paratiroidina."

1905 11 A theory that the placental hormone may cause hyperplasia of the breasts and uterus, independently of the ovaries, advanced by *J. Halban,* of Germany.

1906 1 *J. S. Edkins,* of London, finds a substance similar to secretin in stomach walls and names it "gastrin."

1906 8 Tetany treated successfully by administration of beef parathyroids by *W. S. Halstead,* of Johns Hopkins University.

1906 10 The uterotonic action of a posterior pituitary extract demonstrated by *H. H. Dale,* of London.

1906 16 Portion of a woman's thyroid transplanted to the spleen of her myxedematous daughter by *E. Payr,* of Leipzig, with successful results.

1907 1 Pluriglandular insufficiency first suggested by *H. Claude* and *Henri Gougerot* before the Paris Society of Biology.

1907 7 *A. Loewi,* of Vienna, notes that injections of adrenalin into diabetics cause dilatation of the pupil, suggesting that pancreas secretes substance antagonistic to adrenalin.

1907 8 In experimental tetany following parathyroidectomy, *H. Leischner,* of Germany, abolishes spasms by parathyroid extract, parathyroid feeding, or regrafting the glands. [Confirmed by *W. S. Halstead* (1909).]

1907 9. *O. Marburg,* of Vienna, considers pineal dysfunction to be cause of macrogenitosomia præcox, because teratoma of pineal was found in forty cases that came to autopsy.

1907 12 *Serrallach* and *Pares,* of France, conclude from their experiments that prostate is a gland of internal secretion.

1908 1 *L. Rénon,* of Paris, explains endocrine syndromes requiring associated organotherapy, or *opothérapie associative.*

1908 1 Theory of interrelationship of glands emphasized by Viennese clinicians, *Hans Eppinger, W. Falta,* and *C. Rudinger.*

1908 6 Experiments of *St. Rebaudi,* of Germany, show that removal of the corpora lutea in rabbits is followed by proliferation in the cells of islets of Langerhans; lutein extracts decrease proliferation.

1908 7 *G. Zuelzer,* of Berlin, reduced excretion of sugar in a depancreatized dog with an alcoholic extract of a pancreas removed at the height of digestion.

1908 8 At the Johns Hopkins Hospital, *W. G. MacCallum,* and *Carl Voegtlin* successfully control tetany with calcium salts.

1908 8 Clinical symptoms of myasthenia gravis minutely analyzed by *F. Chvostek,* Viennese neurologist. He attributes this to parathyroid dysfunction, while tetany is caused by hypofunction.

1908 10 *W. Blair Bell,* of Liverpool, confirms Dale's reports on uterotonic action of infundibulin.

1908 10 An experimental pathological reversion to the Fröhlich syndrome, by partial excision of the anterior pituitary in dogs, produced by *Harvey Cushing* at Johns Hopkins Hospital.

1908 10 Negative results obtained by *N. Paulesco,* of Bucharest, in removing posterior pituitary, but he produced results equivalent to entire removal by excision of anterior lobe.

1908 13 A "peristaltic hormone" described by *Zuelzer, Dorhn,* and *Marxer,* of Berlin, who obtained extracts of gastric and duodenal mucous membrane and spleen that excite peristalsis.

1908 16 Interest in metabolism revived by *F. G. Benedict's* use of his new "unit" respiration apparatus in Boston.

1909 10 *W. Blair Bell,* first to utilize posterior pituitary principle, reports original clinical experience with infundibulin in obstetrics.

1909 12 *O. von Fürth,* of Vienna, with *A. Vichnevsky,* suggests that the prostate has an internal secretion.

1910 1 Two opposing diatheses, vagotonia and sympathicotonia, discussed by *Hans Eppinger* and *Leo Hess,* of Vienna. They suggest that a hormone, "autonomin," produced by the pancreas, opposes adrenin, which controls the autonomic system.

1910 2 *W. B. Cannon* and *D. de la Paz,* of Boston, show that "the common excitements of an animal's life were capable of evoking a discharge of adrenin," leading to further considerations of the effect of emotions on adrenal secretion.

1910 5 *C. Trunecek,* of Prague, discussing accouchement of the pygopagous twins, Rosa-Josefa Blazek, reports mammary activity in both twins from pregnancy in one of them.

1910 10 The idea of dyspituitarism, or perversion of function, covering hypo- or hyperfunction, is introduced by *Harvey Cushing,* of Boston, for, as originally observed by *Crookshank* and confirmed by *Cushing,* an acromegalic woman may have a son afflicted with pituitary infantilism or obesity.

1910 15 *M. Lucien* and *J. Parisot,* of Nancy, France, note marked arrest in development of the skeleton following thymectomy.

1910 16 *David Marine* and *C. H. Lenhart,* of Ohio, prevent goitre in hatchery trout by adding iodide to the water.

1911 1 *G. Zuelzer* offers peristaltic hormone (from the spleen) under the name "Hormonal."

1911 1 *I. Ott* and *J. C. Scott,* of Philadelphia, report that extracts of thymus, testes, and prostate provoke contraction of bladder.

1911 8 *I. Greenwald* and *J. Gross,* of New York, prove that a course of parathyroid may extract lime from the tissues.

1911 9 Extensive studies of the pineal gland published by *P. Bailey* and *Smith Ely Jelliffe,* of New York.

1911 10 *Sir E. S. Schafer* and *K. Mackenzie,* of Edinburgh, attribute galactagogue activity to pituitary extracts.

1911 10 *I. Ott* and *J. C. Scott,* confirm galactagogue action of pituitary and other extracts.

1912 10 *H. Cushing* shows there is evidence of pituitary activity in pregnancy and hibernation.

1912 10 The relation of the pituitary to diabetes insipidus shown by *H. Cushing* and associates.

1912 16 *J. F. Percy,* of Galesburg, Illinois, recommends heavy doses of thyroid in nephritis.

1913 1 *Thomas Stephenson,* of Edinburgh (assisted by *Henry R. Harrower*), publishes first entire issue of periodical devoted to endocrinology (*Prescriber,* April, 1913).

1913 7 *Henry R. Harrower* calls attention to the possibility of concentrating a pancreas-stimulating remedy from the tail of the pancreas in preference to the whole gland.

1913 7 *Sir E. S. Schafer* suggests the presence of an internal secretion in the islets of Langerhans, and names it "insulin."

1913 8 The observation of *W. F. Koch,* of Ann Arbor, Michigan, that the urine of parathyroidectomized dogs contains methylguanidine, opens up a new line of investigation.

1913 9 The precocity of development attributed to pineal deficiency is produced by *Charles L. Dana,* of Woodstock, Vermont, and *W. N. Berkeley,* of New York, by adding pineal substance to the blood.

1913 10 *H. Cushing* concludes from experiments that a lesion of the posterior lobe of pituitary is chief cause of diabetes insipidus.

1913 11 *H. Guggisberg,* of Switzerland, reports that extracts of placenta and thyroid contain substances that promote contraction of uterus.

1913 14 Castration of male rats shown by *J. E. Sweet, E. P. Corson-White,* and *G. J. Saxon,* of Philadelphia, to facilitate the "taking" of implanted tumors.

1913 16 *E. Gley* and *A. Quinquaud,* of Paris, observe that thyroid extract stimulates the adrenal secretion.

1914 9 *C. P. McCord,* of Detroit, concludes from work with the pineal that it contains a substance that stimulates growth and development; but that dyspinealism is a pluriglandular involvement.

1914 11 *H. R. Harrower* suggests that the placenta is a source of therapeutic substances of value as a galactagogue and for relief of the vomiting of pregnancy.

1914 14 *G. Frank Lydston,* of Chicago, performs first homograft of testis on himself.

1914 16 Thyroxin separated from the thyroid by alkaline hydrolysis, and so named by *E. C. Kendall,* of Rochester, Minnesota, who considers it the thyroid hormone.

1915 11 *Hermann,* of Germany, finds an active sex-developing principle in the placenta.

1916 1 *H. R. Harrower* founds the Association for the Study of the Internal Secretions, in Detroit, Michigan, May, 1916—the first society for the study of the endocrines—and simultaneously inaugurates *Endocrinology,* the first periodical of its type.

1916 7 A reduction to normal of the blood-sugar level in depancreatized dogs, by intravenous extracts of fresh pancreas, produced by *N. C. Paulesco,* of Bucharest.

1916 8 *D. Noël Paton* and his colleagues isolate guanidine from blood of parathyroidectomized dogs and show that injection of guanidine salts causes a condition similar to the tetany following parathyroidectomy.

1916 10 *T. Brailsford Robertson,* of University of California, isolates tethelin, a growth-stimulating principle from anterior pituitary.

1916 11 *Teresa Bianchini,* of Italy, reports successful use of placenta as a galactagogue.

1917 6 *Robert T. Frank,* of New York, injects follicular fluid into virgin rabbits, causing marked hyperplasia of the uterus.

1917 16 *David Marine,* of Akron, Ohio, commences routine iodine prophylaxis of goitre in school children.

1919 2 *C. E. de M. Sajous,* of Philadelphia, shows that adrenals of influenza patients suffer, and advises adrenal feeding.

1919 2 Autopsies conducted by *D. M. Cowie* and *P. W. Beaven,* at University of Michigan, on victims of influenza, reveal hypoplasia of adrenals and evidence of adrenal dysfunction.

1919 6 *W. P. Graves,* of Harvard, suggests utilization of the portion of ovary remaining after removal of corpus luteum.

1919 14 *Serge Voronoff,* of Paris, publishes results of 120 testicular grafts.

1920 4 *G. H. Whipple,* of University of California, demonstrates marked hemopoietic action following liver feeding in dogs anemic from repeated bleedings.

1920 10 Considerable fruitful experimental work on the pituitary gland conducted by *M. Ascoli* and *Legnani,* of Milan, Italy.

1920 11 Placenta substance, as a galactagogue used by *Bertha van Hoosen,* of Chicago, in thirty-three cases. The results show that it is a powerful stimulant to mammary secretion.

1921 1 *C. E. de M. Sajous* holds the first chair of Applied Endocrinology, founded April 30, 1921, in the University of Pennsylvania.

1921 7 Experimental work with pancreas begun in May, 1921, by *F. G. Banting* and *C. H. Best,* under auspices of *J. J. R. Macleod* at the University of Toronto. First preparations of insulin, made by a water extraction method, enable depancreatized animals to utilize sugar as do normal animals.

1921 8 Parathyroid administered orally in treatment of ulcerative conditions by *H. W. C. Vines* and *W. R. Grove,* of Cambridge. Ulcers were completely healed.

1921 10 *H. M. Evans* and *J. A. Long,* of University of California, demonstrate growth hormone of the anterior pituitary.

1921 14 *L. L. Stanley,* prison physician at San Quentin, California, reports results from mass injections of fresh testicular emulsions.

1921 16 *N. W. Brown,* of Toledo, Ohio, estimates activity of one lobe of the thyroid as compared with that of opposite side by use of electrocardiograph.

1922 8 *A. M. Hanson,* of Faribault, Minnesota, develops the original standardized parathyroid hormone—"the parathyroid-hydrochloric X."

1923 6 *Edgar Allen* and *E. A. Doisy,* of St. Louis, Missouri, report on discovery and partial purification of a hormone from the liquor folliculi of hog ovaries, which produces estrus in spayed mice and rats.

1923 6 *E. A. Doisy, E. Allen,* and coworkers, of St. Louis University, standardize activity of folliculin, the ovarian hormone from the liquor folliculi. The "Doisy unit" represents quantity necessary to produce estrus in sexually mature, ovariectomized rats.

1923 7 *J. J. R. Macleod,* of Toronto, shows that the hypoglycemia produced by insulin can be counteracted promptly by glucose.

1923 7 A practical process of extracting insulin devised by *J. B. Collip,* of Toronto, who employs 95 per cent. alcohol as extraction fluid for minced pancreas. Alcohol inhibits trypsin action.

1923 8 *H. A. Salvesen,* of Oslo, Norway, finds that intensive calcium therapy prolongs life in parathyroidectomized dogs.

1923 8 *H. W. C. Vines,* at Cambridge University, connects low blood calcium with chronic ulceration; paves way for parathyroid therapy in ulceration.

1923 8 *H. H. Scott,* of Hongkong, himself a sufferer from sprue, finds his blood calcium low and cures himself with oral parathyroid therapy.

1923 13 According to *C. D. Leake* and *J. S. Evans,* of University of Wisconsin, red bone-marrow and spleen in equal amounts "were more efficient in promoting hemopoiesis in combination than separately."

1924 3 *Malford W. Thewlis,* of New York, reports beneficial clinical results in treating many cases of senile nephritis with a renal extract of total kidney substance.

1924 4 *W. J. Macdonald,* of St. Catharine's, Ontario, suggests hepatic depressor therapy.

1924 7 *Swale Vincent, E. C. Dodds,* and *F. Dickens,* of London, confirm *J. J. R. Macleod's* opinion that source of insulin is islet tissue of pancreas.

1924 7 *N. F. Fisher,* at University of Chicago, observes that insulin does not represent entire hormone complex, since in absence of pancreas it cannot maintain life or control all diabetic symptoms.

1924 10 *L. Loeb* and *E. E. Kaplan,* of St. Louis, observe that anterior pituitary substance inhibits compensatory hypertrophy of thyroid.

1924 16 The in-vitro experiments of *José Carra,* of Modena University, Italy, show that testicle and thyroid stimulate growth of neoplastic cells.

1925 4 *A. A. James* and *N. B. Laughton,* of University of Western Ontario Medical School, find that liver extract will reduce blood-pressure whether it be high or normal.

1925 4 *Ralph H. Major,* of Kansas City, finds that in normals and in high blood-pressure cases, liver extract produces no toxic effects, and the reduction of pressure is immediate but not lasting.

1925 4 *H. R. Harrower* standardizes a stable solution of the alcoholic fraction of liver, calling it "Anabolin."

1925 8 *I. Greenwald* and *J. Gross,* of New York, conclude from experiments that parathyroid hormone keeps calcium in solution.

1925 8 *H. Dryerre* and *J. R. Greig,* of Edinburgh, prove that milk-fever in cows is a symptom of hypoparathyroidism with the blood calcium at half normal.

1925 12 Experiments of *V. Korenchevsky* and *M. Carr,* of the Lister Institute, London, suggest that the prostate has internal secretion which influences metabolism.

1926 1 *Ludwig Haberlandt,* of the University of Innsbruck, discovers the "heart hormone."

1926 4 *G. R. Minot* and *W. P. Murphy,* of Harvard University, announce control of pernicious anemia by liver feeding.

1926 6 Folliculin, the first physiologically standardized female sex hormone separated from the liquor folliculi, submitted by *H. R. Harrower.*

1926 10 *P. E. Smith,* of Stanford University, conclusively proves that sex development is inhibited by hypophysectomy, while replacement therapy corrects these results.

1926 11 *E. C. Dodds* and associates, at Middlesex Hospital, London, isolate an estrin from the placenta.

1926 16 *C. R. Harington,* of University College, London, establishes chemical constitution of thyroxin and synthesizes it.

1927 1 *H. M. Evans* and *G. O. Burr,* of University of California, isolate the antisterility vitamin *E.*

1927 2 *F. A. Hartman* and associates, at University of Buffalo, isolate adrenal cortex extract, which they name "cortin," and which prolongs life in adrenalectomized animals.

1927 4 Liver extract, as a remedy for pernicious anemia, discovered by *G. R. Minot, W. P. Murphy, H. A. Lawson,* and *E. J. Cohn.*

1927 7 Crystalline insulin produced by *J. J. Abel,* of Johns Hopkins University.

1927 7 *Carl von Noorden,* of Frankfort University, recommends a powdered, condensed extract of the pancreas in tablets for use in diabetes.

1927 8 Three hundred forty-seven cases with hemorrhage given parathyroid injections by *B. Gordon* and *A. Cantarow,* of Philadelphia. Control noted in 304 cases.

1927 11 The female sex hormone or estrin prepared from the placenta and found by *H. R. Harrower* to be experimentally identical with folliculin. It is named "Plestrin."

1928 1 *A. C. Ivy* and *E. Oldberg,* of Chicago, announce cholecystokinin prepared from the duodenal mucosa, a principle that causes contraction and evacuation of the gall-bladder.

1928 2 *Max A. Goldzieher,* of Brooklyn, isolates active principle of adrenal cortex, which he names "interrenin."

1928 2 *J. M. Rogoff* and *G. N. Stewart,* of Western Reserve University, Cleveland, isolate active principle of adrenal cortex, naming it "interrenalin."

1928 11 *A. Butenandt,* of Göttingen, crystallizes an estrin from the placenta which he calls "Progynon."

1928 10 *O. Kamm* and associates, in Detroit, split the posterior pituitary active principle into two parts—one oxytocic in character, the other circulatory in influence and pressor in effect.

1928 11 *J. Kosakaé,* of Japan, finds that a hydrolytic extract of placenta produces contractions of uterus in situ as well as on the removed uterus.

1929 1 *R. H. Major* and *C. J. Weber,* of University of Kansas, find a depressor fraction (not histamine) in brain tissue.

1929 2 *H. R. Harrower* perfects and standardizes a stable epinephrine-free adrenal cortex hormone, calling it "Adreno-Cortin."

1929 7 *E. Gley* and *N. Kisthinios,* of Paris, produce from the pancreas a hypotensive substance called "Angioxyl," with no action on the blood sugar.

1929 10 *H. R. Harrower* prepares an active growth hormone from anterior lobe pituitary, naming it "Accretin."

1929 10 *Leo Loeb,* of St. Louis, confirms previous observation of *E. E. Kaplan* and *Leo Loeb* (1924) that anterior pituitary substance exerts inhibiting effect on compensatory hypertrophy of thyroid.

1929 10 *B. P. Wiesner,* of Edinburgh University, reactivates the testes of senile rats by injections of a gonadotropic hormone from the anterior pituitary.

1929 14 *Casimir Funk* and *B. Harrow,* of New York, isolate the male sex hormone from the urine.

1929 14 *T. F. Gallagher* and *F. C. Koch,* of Chicago University, standardize the male sex hormone.

1929 14 *L. Jacqmin,* of the University of Louvain, concludes that the male sex hormone inhibits metastasis of tar cancer in mice.

1929 15 *K. Glaessner* and *J. Hass,* of Vienna, show that fractures consolidate more rapidly in normal cats than in thymectomized cats. Thymus extract stimulates ossification of callus better than parathyroid or testicular extracts.

1930 1 *M. S. Schwartzman,* of London, reports separation of a principle from muscle which is beneficial in angina.

1930 1 *Walter B. Castle,* of Harvard University, reports overcoming gastric disability in pernicious anemia by feeding meat that has been predigested for an hour in a healthy stomach.

1930 7 *H. Kraut et al.,* of Berlin, isolate a circulatory hormone from the pancreas and name it "Kallikrein."

1930 2 *W. B. Coffey* and *J. D. Humber,* of San Francisco, announce an extract of the adrenal cortex which causes no local or systemic reaction, but which controls pain in cachexia and, within a week, a softening of malignant tumors, and later, sloughing.

1930 2 *L. G. Rowntree* and *C. H. Greene,* at the Mayo Clinic, announce clinical control of Addison's disease with the cortical hormone prepared by *W. W. Swingle* and *J. J. Pfiffner,* of Princeton University.

1930 6 *E. A. Doisy, S. Thayer,* and *C. D. Veler,* of St. Louis, announce the crystallization of the ovarian hormone from the urine of pregnant women, and name it "Theelin."

1930 10 *H. B. van Dyke* and *Z. W. Lawrence,* of University of Chicago, prepare and assay a growth hormone from the pituitary which they call "phyone."

1930 10 *B. P. Wiesner* and *F. A. E. Crew,* of Edinburgh, conclude from experiments that the follicle-stimulating hormone and the luteinizing hormone of the anterior pituitary are separate and distinct. They also believe in a fourth hormone of the anterior pituitary—a metamorphic factor, thyreotropic in action.

1930 11 *J. B. Collip,* of McGill University, purifies and concentrates active principle of placenta. He calls it "the hormone of pregnancy." It is ovary-stimulating, active by mouth.

1930 13 *J. C. Brougher,* of Vancouver, Washington, connects the spleen with the parathyroid control of calcium by feeding spleen to splenectomized dogs.

1930 14 *S. Loewe et al.,* of Dorpat, Esthonia, separate androkinin, a male sex hormone, from healthy urine.

1930 14 *E. C. Dodds* and associates, of London University, isolate from the testes a water-soluble principle similar to estrin, which stimulates comb growth in capons.

1930 15 *A. M. Hanson,* of Faribault, Minnesota, announces a thymus extract for treatment of cancer, named "karkinolysin." Experiments indicate a selective action in carcinoma.

1931 1 *George A. Wyeth,* of New York, announces a serological test of cancer, pregnancy, and sex determination, using hormone organ antigens.

1931 5 Eighteen cases of bleeding nodular uterus successfully treated by *Louis Berman,* of New York, with daily injections of mammary extract. Twelve cases of painful breasts with nodules successfully treated with corpus luteum.

1931 5 *Max Cutler,* of New York, connects mastodynia with dysovarism and recommends ovarian residue as of constant value.

1931 6 *H. T. Graber* and *R. A. Cowles,* of Detroit, biologically standardize the luteal antestrin.

1931 6 *E. A. Doisy* and *S. A. Thayer,* of St. Louis University, extract a second estrogenic substance from the urine of pregnant women, calling it "theelol."

1931 11 *J. B. Collip,* of McGill University, separates "an anterior-pituitary-like gonad-stimulating hormone" from human placenta.

SUBJECT INDEX OF DATES

1. *General*—*B.C.* 1800, 1500, 460. *A.D.* 20, 60, 200, 1773, 1776, 1801, 1843, 1844, 1852, 1860, 1868, 1881, 1891, 1902, 1903, 1906, 1907, 1908, 1910, 1911, 1913, 1916, 1921, 1926, 1927, 1928, 1929, 1930, 1931.
2. *Adrenals* — 1563, 1628, 1849, 1855, 1856, 1894, 1895, 1896, 1898, 1900, 1901, 1903, 1904, 1910, 1919, 1927, 1928, 1929, 1930.
3. *Kidneys*—1869, 1892, 1893, 1924.
4. *Liver*—1848, 1855, 1857, 1905, 1920, 1924, 1925, 1926, 1927.
5. *Mammary*—1895, 1897, 1905, 1910, 1931.
6. *Ovaries* — 1573, 1776, 1872, 1896, 1899, 1903, 1904, 1908, 1917, 1919, 1923, 1926, 1930, 1931.
7. *Pancreas* — 1877, 1886, 1889, 1891, 1893, 1895, 1901, 1902, 1907, 1908, 1913, 1916, 1921, 1923, 1924, 1927, 1929, 1930.
8. *Parathyroids*—1815, 1851, 1864, 1880, 1890, 1892, 1895, 1896, 1897, 1905, 1906, 1907, 1908, 1911, 1913, 1916, 1921, 1922, 1923, 1925, 1927.
9. *Pineal*—1898, 1907, 1911, 1913, 1914.
10. *Pituitary* — 1543, 1705, 1761, 1772, 1776, 1778, 1781, 1783, 1838, 1840, 1864, 1877, 1884, 1886, 1892, 1894, 1895, 1898, 1901, 1906, 1908, 1909, 1910, 1911, 1912, 1913, 1916, 1920, 1921, 1924, 1926, 1928, 1929, 1930.
11. *Placenta*—*B.C.* 500. *A.D.* 1898, 1905, 1913, 1914, 1915, 1916, 1920, 1926, 1927, 1928, 1930, 1931.
12. *Prostate*—1907, 1909, 1925.
13. *Spleen*—1908, 1923, 1930.
14. *Testes*—*B.C.* 1700, 400. *A.D.* 70, 1762, 1849, 1850, 1889, 1891, 1895, 1913, 1914, 1919, 1921, 1929, 1930.
15. *Thymus* — 1614, 1830, 1838, 1855, 1889, 1902, 1904, 1910, 1929, 1930.
16. *Thyroid*—70, 500, 900, 1180, 1530, 1543, 1552, 1656, 1786, 1789, 1802, 1825, 1829, 1835, 1838, 1840, 1850, 1856, 1873, 1877, 1878, 1882, 1883, 1884, 1886, 1888, 1890, 1893, 1895, 1897, 1901, 1903, 1906, 1908, 1910, 1912, 1913, 1914, 1917, 1921, 1924, 1926.

3. ENDOCRINE PHYSIOLOGY

The Discovery of the Hormones—Chemical Coordination—Hormone Catalysis—The Accepted Endocrine Glands—The Secondary Endocrines—The Other Supposed Endocrines—An Every-Day Matter.

THE SCIENCE of the internal secretions is based on the remarkable physiological faculty of certain body structures to produce internal secretions, or hormones. These "chemical messengers," carried by the body fluids, reach remote structures and there arouse physiological reactions that they are peculiarly capable of bringing about.

We are indebted to a very large number of workers for our present conception of endocrinology; in fact, it would seem that more research has been done in recent years along these lines than in almost any other branch of medicine.

THE DISCOVERY OF THE HORMONES—The principle of hormone action first called a "peripheral reflex secretion," was discovered in 1902 by the experiments of W. M. Bayliss and E. H. Starling (*Lancet,* 1902, i, p. 813) in the research laboratory of University College, London. While studying the then newly discovered enterokinase, these investigators proved that the presence of an acid, or acid stomach contents, in a loop of the small intestine was always followed by a secretion of pancreatic juice. This occurred notwithstanding the careful destruction of all nerve channels. Some of the details of the study and the action of the first-named hormone, secretin, will be found in Chapter 10.

Soon after this the so-called "mamma hormone" was demonstrated in the same laboratory by Starling and his assistant, Miss Lane Claypon (*Proc. Roy. Soc. Med.,* 1905-6, lxxvii, p. 505). It seemed necessary to choose a term to cover these chemical agents, which, when carried by the blood, serve to coordinate the activities of certain remote organs. Starling, therefore, suggested the term "hormone," from the Greek *ὁρμάω,* "I arouse or set in motion." In the years that have followed, innumerable experiments have proved the soundness of Starling's bold premise, and have firmly established, in physiology as well as in therapeutics, the "hormone theory," as it was once called.

The hormones are definite chemical substances, produced either with a special predestined action or as by-products in the normal cell catabolism. They unite the complex activities of the body into a functional harmony, both by chemical regulation effected through the blood stream and, in certain cases, by a reflex control exerted through the autonomic nervous system.

CHEMICAL COORDINATION—In one of Starling's earliest papers on the subject, is found a profoundly interesting and illuminating consideration of the chemical coordination of the activities of the body (*Sc. Progr.*, 1906-7, i, p. 557). In this article the author refers to the excitatory substances (*Reizstoffe*), long familiar to botanists, which have a decided dynamic effect on the living cell. In this respect they present a close analogy to the substances that form the ordinary drugs of our pharmacopœias. One can do no better than to quote Starling's own epoch-making words:

"Since, in the normal functioning of the body they [the hormones] have to be discharged at frequent intervals into the blood stream, and carried onward by this to the organ on which they exercise their specific effect, they cannot belong to that class of complex bodies which include the toxins of animal or vegetable origin. We must therefore conceive the latter as substances of definite chemical composition, and comparable in their chemical nature and mode of action to drugs of specific action such as the alkaloids. This conclusion is borne out by the few investigations which have been made as to the nature of the chemical messengers in the case of certain well-marked correlations of function in the higher animals. In consequence of the distinctive features of this class of bodies, and the important functions played by them in the higher organisms, I have proposed to give a special name to the class—*viz.*, hormones, from *ὁρμάω*, 'I arouse or excite.'"

HORMONE CATALYSIS—The hormones, then, are chemical catalytic agents that initiate certain physiological responses. D. Noël Paton, of Glasgow University, has aptly called them "the chemical regulators of the body." They do, indeed, regulate practically all the reactions involved in growth, nutrition, reproduction, and detoxication.

This was the beginning of hormone therapy, the scientific explanation of that system of animal medication so steadfastly believed in throughout the ages. It would appear that the body manufactures its own drugs, which are supplied by the glands of internal secretion. Not only have they the power to correlate and coordinate the various body functions—such as pregnancy and mammary secretion, growth and sexual development, etc.—but they also destroy toxins, and, further still, these hormones control one another. The essential importance of this will be emphasized more thoroughly in later chapters.

How close the earlier students were to the essentials of hormone action is shown in a paper by Brown-Séquard and his assistant, A. d'Arsonval (*Arch. de physiol. norm. et path.*, 1891, xxiii, p. 747):

"These special soluble products [of the living cell] enter into the blood and serve to influence, with this liquid as the intermediary, other cells or anatomical elements of the organism. As a result, the diversified cells of the

economy are thus correlated with one another by means of a mechanism other than the influence of the nervous system."

By some, endocrinology is considered to be the study of the diseases of the endocrine organs and their effects on the body, but it really comprehends much more. As the reader will find repeated many times throughout this volume, a functional disturbance of endocrine activity is fully as important as an actual endocrine disease; and the minor dyscrinisms are of greater clinical importance than the major ones, if only for the very good reason that they occur so much more frequently and are much more likely to respond to treatment.

The term "endocrine glands" has taken the place of "ductless glands," for several glands with a duct are as much glands of internal secretion as are those without ducts—for example, the pancreas.

THE ACCEPTED ENDOCRINE GLANDS—The known and accepted endocrine organs are the adrenals, gonads, pancreas, parathyroids, pituitary, and thyroid. Each of these produces one or more incretory principles necessary to the normal functioning of the body. Following the removal of each, quite uniform changes result. The artificial deficiency can be compensated—wholly or partially—by feeding, injecting, or transplanting material from the corresponding gland of the same or other species of animals. These are the criteria on which the "acceptable" character of an endocrine organ depends.

Clinical defects in the endocrine organs follow certain quite definite courses and also respond in varying degree to the oral, intramuscular, or intravenous administration of desiccations, concentrates, extracts, or active principles from the corresponding glands. In certain instances, transplanted tissue will serve a somewhat similar purpose, though transplantation is not done so frequently in a clinical as in an experimental way; and such "takes" as may be secured do not persist very long.

THE SECONDARY ENDOCRINES—There are other organs with just as real incretory functions as the accepted endocrine glands. Like such glands as the pancreas, a vital part of the digestive system, which, in addition to its all-important Langerhansian internal secretion, produces an acinous product containing the active digestive ferments—trypsin, amylopsin, and steapsin—they perform more than one service. These secondary endocrine structures are the duodenum, which produces secretin, an accepted hormone (the original hormone, by the way); the liver, which produces the anabolic or detoxicating hormone; the placenta, which stores or produces the spectacular

female sex hormone, and from which several other active principles are now obtained; and the thymus, about which discussion as to its true endocrine character has waxed and waned these many years. There is no longer much disposition to oppose the acceptance of these glands as true components of the endocrine system.

THE OTHER SUPPOSED ENDOCRINES—There are some workers who believe that hormones are produced also by the heart, mammæ, pineal, prostate, and spleen. These organs, with the probable exception of the pineal, are also organs of dual service, ranging in vitalness from the all-essential heart to the spleen, without which life seems to proceed quite normally.

Most of the recorded research with the organs of internal secretion has dealt with replacing or augmenting the physiological functions that depend upon, or are influenced by, their active principles. For this reason the original list of accepted glands of internal secretion has had to be extended from time to time.

Practical endocrinology no longer is concerned merely with the study of the ductless glandular diseases, nor with the clinical possibilities of their hormones alone, but with *every active principle* with endocrine characteristics that can be used to enlarge our professional service to humanity in the control of those physiological functions that have been found to respond to these subtle hormone influences.

AN EVERY-DAY MATTER—Bearing in mind that there is a wide difference between the physiologist's and the clinician's appreciation and attack of a biologic study, let it be said that the physiologist's purpose is to obtain knowledge, while the clinician's main object is to mitigate or cure disease.

So let us proceed with the consideration of endocrinology *as an every-day matter*, not as the specialist, or the physiologist, or the research worker, but as practising physicians, and we shall soon find ourselves in agreement with my mentor, Sajous, who once said (*New York Med. Jour.*, Feb. 20, 1915, cl, p. 364):

"Gradually, as the functions of the internal secretions are being investigated, their influence, beneficial and morbid, on diseases other than those of the ductless glands themselves is being increasingly recognized. . . . Strictly speaking, however [endocrinology], interpreted as designating a specialty, should be reserved for disorders of the glands per se, or in which these organs play the preponderating etiological rôle. While its scope, thus restricted, would seem to include but a few relatively uncommon diseases, in reality it will embrace not only a very broad field, but one fraught with incalculable possibilities for good."

4. ENDOCRINE RELATIONSHIPS

A CONSIDERATION of the endocrine relationships must be prefaced with an explanation. We know that certain endocrines function in a stated cooperative way, and these relationships are the ordinary ones that will be listed. But it is undoubtedly possible for certain endocrine glands in times of stress and physiological irregularity to be so disturbed as to appear to be antagonizing instead of cooperating. They may even "fight," and without a doubt some of the physiological experimental work is done under conditions sufficiently far away from the norm to explain contradictory reports which at times seem to vitiate the general conclusions.

	Cooperation	*Antagonism*
1. THYROID	Adrenals, Pituitary, Gonads, Liver	Thymus, Pancreas, Parathyroids, Mammæ (lactating)
2. PITUITARY	Thyroid, Gonads, Mammæ, Adrenals	Pancreas, Duodenum
3. ADRENALS		
Medulla	Thyroid	Pancreas, Duodenum
Cortex	Gonads, Pituitary	Thymus, Gonads, Parathyroids
4. PARATHYROIDS	Pancreas, Liver, Gonads	Thyroid
5. GONADS	Thyroid, Adrenals, Pituitary	Thymus, Mammæ, Pancreas, Pineal
Corpora Lutea	Mammæ, Placenta	Follicle
6. PANCREAS	Liver, Parathyroids, Duodenum	Adrenals, Gonads (F), Pituitary, Thyroid
7. THYMUS	(?)	Adrenals, Gonads, Thyroid
8. PINEAL	(?)	Gonads, Pituitary
9. LIVER	Thyroid, Parathyroids, Pancreas, Duodenum	(?)
10. PLACENTA	Corpora Lutea, Mammæ	Follicle
11. DUODENUM	Pancreas, Liver	Adrenals, Pituitary
12. MAMMÆ	Pituitary, Placenta, Adrenals, Corpora Lutea	Gonads (F)

It is difficult to portray in an inflexible table or diagram a mind-picture of the hormonic actions and interactions. Not always does a hormone or the gland from which it originates act identically under different conditions. As will be seen in the chapter on "Etiological Factors" (26), many circumstances control the influences exerted by the endocrine glands upon one another and upon the body as a whole. One can, however, roughly show the generally accepted and principal actions of the various endocrine glands, and this has been done in the table on the preceding page and in the chart on the next page.

From the foregoing tabular outline it will be clear that the majority of the endocrine glands divide themselves into two cooperative classes or systems that appear to balance each other. These are (1) the *sympatheticotonic* or *catabolic* glands, including the adrenals, thyroid, pituitary, and gonads; and (2) the *vagotonic* or *anabolic* glands, including the pancreas, parathyroids, and, perhaps, the liver. The sympathetic nervous system, being catabolic, produces kinetic energy. It also raises the amount of sugar in the blood to provide energy for defense against (a) the external foe by flight or fight, (b) the internal foe of bacterial invasion by pyrexia. The parasympathetic or vagotonic nervous system, being anabolic, stores potential energy. It therefore cooperates with the digestive system, which obtains energy for the body from the food and diminishes the amount of sugar in the blood, storing it in the tissues.

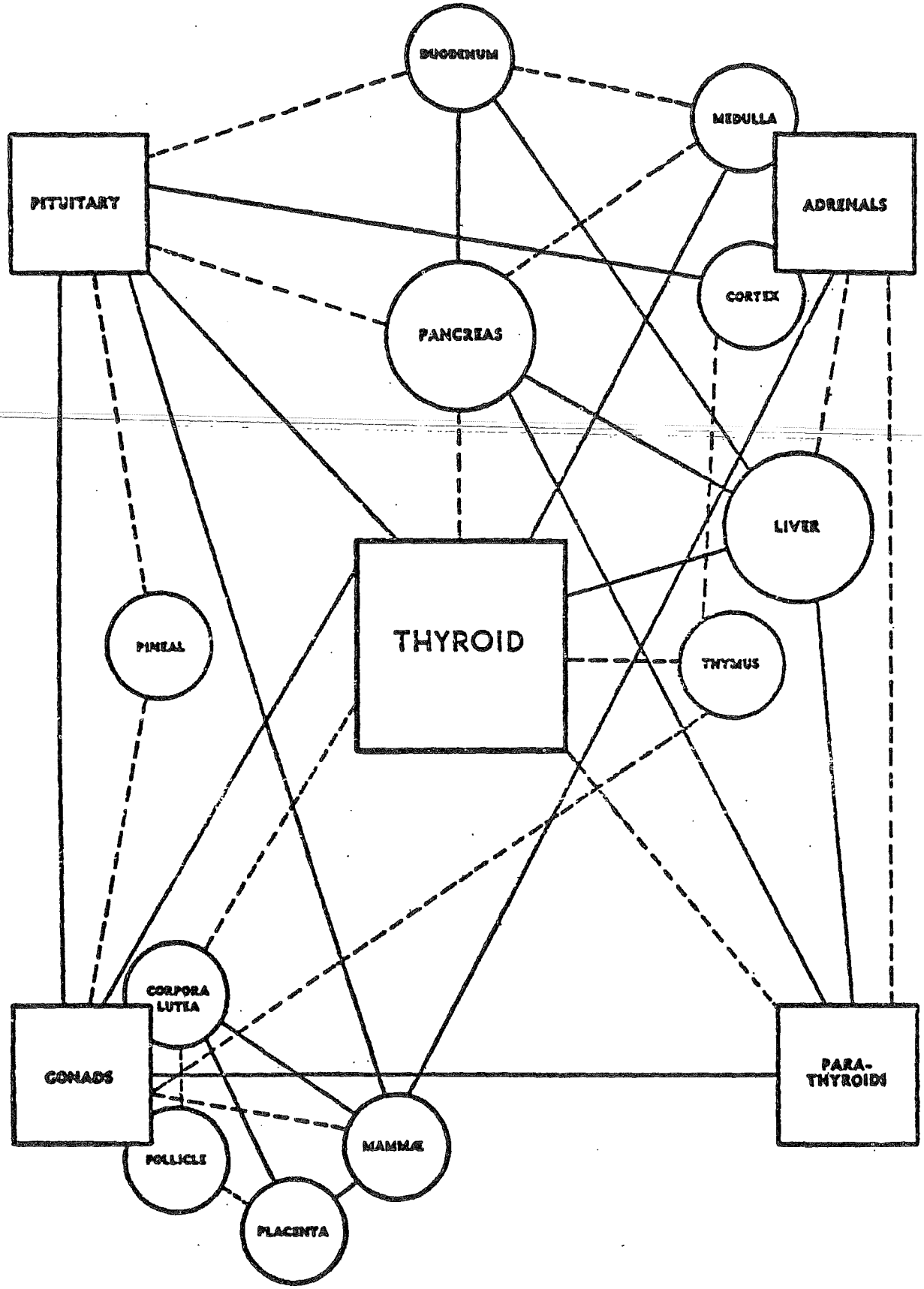
According to W. Langdon Brown, of London ("The Endocrines in General Medicine," London, Constable & Co. Ltd., 1927, p. 11), the adrenals, thyroid, and pituitary are predominantly catabolic and cooperate with the sympathetic division of the autonomic nervous system. They also cooperate with the gonads. On the other hand, the islet cells of the pancreas (Langerhansian) and the parathyroids are predominantly anabolic as is the parasympathetic division (vagus) of the autonomic nervous system.

The question has been asked: "Is the liver to be included with the vagotonic group because one of its important hormone functions is anabolic?" And it appears that, in view of the new knowledge that we now have regarding the detoxicative function of the liver, the answer will have to be in the affirmative.

These essential endocrine interrelationships were visualized in the following schematic chart that originally appeared in my first book on endocrine matters ("Practical Hormone Therapy," London, Baillière, Tindall & Cox, 1914). It has been redrawn and brought up to date, and should require no further explanation.

The Relations of the Endocrine Organs

(Schematically arranged)



5. THE PLURIGLANDULAR BALANCE

Intercellular Equilibrium—Origin of the Pluriglandular Idea—Two Types of Pluriglandular Disease—The Uniglandular Origin of Pluriglandular Syndromes—Opposition Based on Misconception—A Personal Experience—Further Confirmation.

THE HORMONE balance is mentioned repeatedly in these pages. It forms the basis of practical endocrinology and is essential to the normal physiological functioning of the organism.

INTERCELLULAR EQUILIBRIUM—From our present knowledge of the endocrines, which has accumulated rapidly during the last forty years, the intimacy of the endocrine interrelations stands out above all.

A quotation is submitted from "Practical Hormone Therapy" (page 28) to emphasize the interrelationship of the endocrines:

"In the body every motive force is balanced by a retarding force, and this nice equilibrium is quite essential to the proper regulation of the numerous cellular functions. Should one of two factors gain the ascendency, disorganization may be expected at once, and the extent of this disturbance can hardly be confined to the single area in which it is initiated. This is evidently what happens in diabetes, myxedema, acromegaly, ovarian insufficiency, and numerous other conditions related to the internal secretory system. If we are able partly or wholly to restore that balance by the addition of a suitable agent in the form of an animal extract or hormone, we shall have assisted Nature in a very effective and helpful manner.

"Numerous writers have considered the close interrelation between the internal secretions, and have demonstrated that certain of these secretions are synergists, while others are antagonists. Bearing in mind the altruistic function of the cell—that function which influences its near or remote neighbors—the importance of the hormone equilibrium may be faintly appreciated."

The endocrine balance is evidently maintained by a cooperation of different groups of endocrine glands that enable the physiological processes to go on smoothly. We often speak of the antagonism and synergism that exist between certain glands, but the relation of *hormone* (stimulating principle) and *chalone* (retarding principle) is not accurately expressed in terms of antagonism, which connotes a certain hostility. However, since *antagonism* and *synergism* are current phraseology, they will be employed here. An instance of such an antagonism is found in the relation of the thymus to the gonads. In a discussion of this matter, Adolph Jacoby, of New York (*New York Med. Jour.*, Feb. 5, 1921, cxiii, p. 243), says:

"During its [thymus] period of growth, the ovaries do not function. As the thymus atrophies the ovarian function becomes manifest; menstruation

begins, and the secondary sex characteristics become evident. Feeding thymus extract to frog larvæ causes an increase in their growth, but no differentiation. The removal of the thymus in animals causes an increase in the weight of the testes or ovaries. The removal of the testes or the ovaries, on the other hand, causes an increase in the thymus. From these experimental and physiological observations it becomes evident that there is a direct antithesis in the action of these glands; that when the function of the one is in evidence that of the other is in abeyance and vice versa."

ORIGIN OF THE PLURIGLANDULAR IDEA—We have just seen that certain of the endocrine glands definitely cooperate with one another, while others antagonize or balance them (4). The pluriglandular idea dawned in France in the first few years of this century (2). On December 28, 1907, H. Gougerot and Henri Claude, of Paris (*Compt. rend. Soc. de biol.*, 1907, lxiii, p. 785), reported their findings "Sur l'insuffisance simultanée de plusieurs glandes a sécrétion interne" to the Paris Society of Biology. The essence of their conception was stated thus:

"We conclude from a study of our case that it is possible to observe a clinical syndrome, the characteristics of which are the same as those exhibited in the symptomatology of the various glandular insufficiencies, with predominance of the characteristics of certain of these insufficiencies in relation to the severity of the respective disorders. The peculiar characteristic of this syndrome is the simultaneous association of the symptoms of a different origin, but developing under the influence of another cause which, in our own case, appears to be tuberculosis. In a word, we are of the opinion that, together with the syndromes of insufficiency—thyroid, testicular, adrenal, etc.—the existence must be admitted of a syndrome of simultaneous insufficiency of several incretory glands, the syndrome of pluriglandular insufficiency."

These writers later published a comprehensive explanation of their new method of treating endocrine disorders by pluriglandular therapy ("Syndromes pluriglandulaires, délimitation des syndromes d'insuffisance et d'hyperfonctionnement pluriglandulaires," *Gaz. d. hôp.*, 1912, Nos. 57, 60).

TWO TYPES OF PLURIGLANDULAR DISEASE—According to Hermann Zondek, of Berlin ("Krankheiten der endokrinen Drüsen," Berlin, Julius Springer, 1926, p. 366), endocrine diseases, in the majority of cases, are not due to pathological changes in single hormone glands, but must be looked upon as pluriglandular disturbances. When speaking of pluriglandular insufficiency, however, this author does not refer to those maladies wherein the primary trouble has obviously come from a single gland (*e.g.*, Graves' disease, myxedema, acromegaly, gigantism, even *dystrophia adiposogenitalis*), but to those conditions in which early symptoms appear simultaneously, or in quick succession, that point to several glands.

While Zondek refers to the pluriglandular insufficiency previously described by Claude and Gougerot, he has in mind more especially a syndrome described by Wilhelm Falta, of Vienna ("Die Erkrankungen der Blutdrüsen," Berlin, Julius Springer, 1928, p. 427), as a "multiple blood-gland sclerosis." Falta believes that various factors, perhaps always infectious processes, involve several endocrine glands simultaneously, causing sclerosis with resultant symptoms of glandular deficiency. The pituitary, thyroid, adrenals, and gonads are most frequently affected; less often, the parathyroids. A general cachexia is the most striking feature of the clinical picture.

Falta also sees evidences of pluriglandular insufficiency in certain cases of idiocy, where faulty development of the central nervous system is associated with dwarfism, eunuchoidism, and cachexia.

Cases have been described in which obesity, myxedema, genital atrophy, and scleroderma coexisted, the pluriglandular insufficiency presenting the most divergent and variable clinical pictures, sometimes very difficult to interpret.

THE UNIGLANDULAR ORIGIN OF PLURIGLANDULAR SYNDROMES—The presidential address by Hans Lisser, of San Francisco, read before the twelfth annual session of the Association for the Study of Internal Secretions, June, 1928, carried the foregoing title and was published in the Biedl-Festschrift (*Endokrinologie,* 1929, v, p. 138). Since Lisser's conception of the subject is accepted by many, I am quoting several paragraphs:

"This is the practical lesson which experience teaches the clinician who would strive not to lose his way in the pluriglandular underbrush. It is true that some of the trails are difficult to follow and seem to lead nowhere; but years of labor have resulted in many fair roads, and some paved highways. In planning jaunts in endocrinology it will be safest, for the most of us, to stick to the well-known uniglandular highroads, with clearly labeled diagnostic sign-posts. . . . The several ductless glands taken together form an interrelated and to some extent interdependent system, the so-called 'hormonopoietic system' (Falta). Although it is presumed, and probably correctly, that each gland furnishes a secretion which is unique for itself and not duplicable by any other gland or tissue in the body, it does not follow that each gland is sufficient unto itself alone. Functional upheaval in any one gland of the system does not ordinarily permit of normal function in the remainder, but involves one or more of them in its tribulations, and may even evoke an attempt to assist the damaged member by exaggerated compensatory response. . . .

"In the enthusiasm for roping these glands together, a veritable jungle of knots has been tied that is difficult to untangle. This glandular jugglery has created a subtle danger when applied to organotherapy, for the doctrine of pluriglandular disease has led to the doctrine of pluriglandular therapy, with the introduction of shotgun-hit-or-miss mixtures. . . . As a matter of fact,

the overwhelming majority of endocrinopathies which we are justified in diagnosing, exhibit a predominantly uniglandular basis, which any one properly trained in endocrine diagnosis should be able to recognize. This conception (for which no originality is claimed) is a fundamental and controlling basis for the proper interpretation of endocrine syndromes. . . .

"The great majority of endocrine syndromes originate and develop in the chain-store manner. They arise, quite unmistakably, in a single ductless gland and subsequently become more elaborate as disease of this gland evokes disturbed function in one or more other glands. Such clinical complexes have a predominantly uniglandular basis, and the manifestations of perturbed activity of the original gland overshadow the subordinate effects of the glands secondarily affected. If we abandon these clearly outlined pictures, which point boldly and plainly to the gland primarily responsible, and adopt in their place vague and foggy sketches of pluriglandularism, endocrine diagnosis will lose whatever precision has been laboriously acquired and become a blurred impressionistic muddle. . . . It is admitted that almost all incretory syndromes partake of the nature of pluriglandularism. But even though this be true, and even though two or three or four glands are eventually implicated, a searching anamnesis and a scrutinizing physical examination will ordinarily reveal the gland originally attacked, whose dysfunction created the disturbance and because of which other glands became secondarily embroiled."

While there are many pluriglandular dyscrasias that have an essentially uniglandular origin and exhibit a preponderance of effects of the original dyscrinism, it is very unlikely that such a case will present itself for treatment in time to avoid compensatory reactions on the part of the associated glands. It also seems to me quite impossible for a cause of endocrine upset which is general in nature, as an acute infectious disease or a chronic infection or toxemia, to so single out a given endocrine gland that its effects are essentially uniglandular.

In the practice of medicine, we are not concerned with theoretical considerations; we must not depend even upon the text-books, whose writers demonstrate only the clear-cut and the distinctive endocrinopathies so that we may understand them the more simply.

But it must be admitted that the failures so often encountered in the practice of endocrinology far too often are due to the overlooking of associated factors. Let us therefore treat the original and obvious uniglandular disorder, but let us also treat the associated pluriglandular disorder.

OPPOSITION BASED ON MISCONCEPTION—Despite varying opinions about the reasonableness of this whole idea, it has met with much opposition, which has been emphasized in no uncertain terms. For instance, in a paper in the *Journal of the American Medical Association* (Jan. 21, 1922, lxxviii,

p. 181) entitled "The Ovary and the Endocrinologist," Robert T. Frank, of New York, says:

"The ovary exerts a powerful influence on both the primary development of the female sex organs and their function during sexual life. Whether other glands of internal secretion affect the sexual sphere, except secondarily, that is, by the intermediation of the ovaries, is more than doubtful. For example, the claims of Goetsch that anterior lobe pituitary extract stimulates the growth of the sex organs was disproved by me in 1918 and more recently again by Sisson and Broyles. Yet this supposititious pituitary influence continues to crop out in the literature and in the 'therapeutic' advertising pamphlets with which the medical profession is bombarded."

It may properly be mentioned here that "the claims of Goetsch, that anterior lobe pituitary extract stimulates the growth of the sex organs" are now confirmed on all sides, and, as the reader will see (18), the function of this particular gland is now considered to be inextricably related with that of the ovary. J. B. Collip, of Montreal (*Can. Med. Assn. Jour.*, Feb., 1930, xxii, p. 212), also expressed a view entirely opposite to that apparently held by Frank when he asserted that

"The phenomenon of ovulation is in large measure controlled by the secretion of the anterior lobe of the pituitary gland."

A PERSONAL EXPERIENCE—It happens that my own life has been shaped by a chance discovery that, therapeutically, we were far behind the French clinicians, especially in regard to the endocrines and organotherapy. When in Paris in 1913, I learned that Prof. Paul Dalché, one of the principal gynecologists in the university there, had a rule at his clinic at the Hotel Dieu that all patients who received ovarian therapy should also have a dose of thyroid, with the exception of those with frank hyperthyroidism. On returning to the United States, I began to add thyroid to my ovarian and luteal prescriptions, and was astounded at the advantage thus secured. Dalché's work and writings so widened my view of ovarian irregularities as to suggest that, since thyroid supplements ovarian therapy so remarkably, these cases might well be considered from the pituitary standpoint also, inasmuch as the pituitary is involved with the thyroid. The answer was obvious to me, and so pituitary was added. The resultant formula was later (1918) made generally available, and it is known as Thyro-Ovarian Co.*

The thyroid-ovarian-pituitary relationship is but one of the endocrine intimacies; several others have been discovered and this knowledge advantageously applied. That the menopause is a pluriglandular upset has been proved both experimentally and clinically, with the therapeutic success which was logically to be expected.

FURTHER CONFIRMATION—Since March, 1916, when I first took an aggressive stand on this matter, many confirmations of the pluriglandular idea have appeared in the medical literature. For example, Oliver T. Osborne, Professor of Therapeutics at Yale University (*New York Med. Jour.*, Sept. 7, 1918, cviii, p. 401), says:

"Ovarian secretion is always abnormal in thyroid subsecretion. Also the ovaries are overstimulated in thyroid hypersecretion. In thyroid insufficiency the skin is dry and coarse; in pituitary insufficiency, if the thyroid is not also much disturbed, the skin is moist and soft. In both conditions, as just stated, there is likely to be amenorrhea. Thyroid disturbance is far more frequent, about 80 per cent. of all cases, in women than in men. . . . The thyroid is typically a female gland, entering constantly into the woman's sexual life. Menstruation cannot properly occur without the activity of the thyroid. . . . Many of the disturbances of the menopause are due to too much or too little thyroid secretion."

Again, the London gynecologist, Leonard G. Phillips (*Brit. Med. Jour.*, Sept. 27, 1924, p. 563), agrees not only that the endocrine relations are important but that pluriglandular therapy is rational:

"The administration of extracts of ductless glands is sometimes extremely encouraging. In some cases, remarkable results are produced in a most dramatic manner, and patients are deeply grateful for relief. Cases with long and irregular intermenstrual periods and scanty flow sometimes derive much relief from combined extracts of ductless glands, especially thyroid, ovary, and pituitary. Again and again in such cases, the administration of polyglandular extracts is followed by regulation and stabilization of the periods."

More recently in the *Journal of the American Medical Association* (May 30, 1931, cxcvi, p. 1893), the editor remarks:

"The ovaries are, of course, essential for menstruation and pregnancy, but other glands of internal secretion play an important part in these processes. The most vital one of the other glands is most likely the hypophysis, but the thyroid is likewise important. The hypophysis has been called the 'motor of the ovary' because of its domination of the ovaries. In cases similar to the one mentioned, good results *seem* to have been obtained in some cases by oral administration of preparations of the anterior lobe of the pituitary or thyroid preparations *or both*. . . ." (The italics are my own.)

Numerous other items might be marshalled here, of which the following is of special interest. In *Endocrinology* (Nov.-Dec., 1925, ix, p. 479), H. Lyons Hunt, of New York, submitted the thesis that "the testicular hormone is not entirely responsible for all the functions attributed to it," but that "the prostate is definitely responsible, with the testicle, for both sex function and sex desire." Hunt adds that his conclusion is supported by clinical proof that has been confirmed again and again (20).

6. THE BASIS OF ORGANOTHERAPY

"The Drugs of the Body"—Substitutive Organotherapy—Homostimulative Organotherapy—Symptomatic or Specific Organotherapy—Empirical Organotherapy—Endocrine Catalysis—Clinical Improvement a True Criterion—Opposition to Organotherapy—How Shall We Measure Dosage?—The Pluriglandular Idea—Protecting Extracts from Digestion—What Is "A Fair Trial"?

AN APT and vivid statement was made by H. H. Dale, Secretary of the British National Research Council, before a scientific gathering in 1926.

"THE DRUGS OF THE BODY"—Here is a small part of Dale's statement that will serve to introduce the subject of this chapter and to impress its importance:

"Physiology has revealed the presence in the animal body of organs constantly making and adding to the blood substances rivalling the most potent of the alkaloids in the intensity of their action, in modifying, stimulating, depressing, or regulating the activity and metabolism of the body and its organs. Already preparations of these hormones, the natural drugs of the body, play a large part in the treatment of disease and in the maintenance of health and normal development. . . . No branch of modern therapeutics can show triumphs more genuine or more dramatic."

The formulation of the internal-secretion theory and the results of the purely physiological investigations gave a firm basis to one of the oldest and most empirical forms of treatment, as expressed by Artur Biedl, of Prague ("The Internal Secretory Organs, Their Physiology and Pathology," London, John Bale Sons & Danielsson, Ltd., 1919, p. 20):

"This method is founded upon the assumption that the internal secretion elaborated by an organ is contained in the tissue of that organ and, more particularly, in the juice expressed therefrom. It was thought that, even though the actual amount of active substance present in the organ must necessarily be small, yet, in view of the extreme activity of the extract, it must be possible to obtain all the effects of substitution, especially if the administration was continued over a long period of time. The brilliant results of organotherapy in the pathological conditions due to suppression of the thyroid, amply prove the justice of this theory. Similar results, though by no means so striking, have been obtained in connection with other organs; while in the case of yet others, the extract of the organ in question, whether given by mouth or by injection, produced but unimportant and, in some instances, barely perceptible, effects."

It is possible by the administration of glandular extracts to influence physiological function so as to modify the course of disease. Since this is a way in which the body itself fights disease, it is evidently a natural method.

There are four types of organotherapy, the understanding of which is a prerequisite to their successful application.

SUBSTITUTIVE ORGANOTHERAPY—The name of the first is self-explanatory. Correctly prepared extracts of various glands supply to the corresponding organs of the subject the physiological secretions that these glands lack, whether owing to absence, atrophy, or functional inactivity. This was the first form of organotherapy to be practised. As J. T. Halsey, of New Orleans, says in "Endocrinology and Metabolism" (Vol. I, p. 81):

"At first it was believed that such glandular preparations could act only substitutionally, that is, that the substances administered acted in place of the absent or diminished secretion of the patient's gland, but very soon it became apparent that all the results obtained could not be explained so simply, and that there must be other modes of action."

The action of insulin in diabetes (15) is one of the best illustrations of this replacement therapy.

HOMOSTIMULATIVE ORGANOTHERAPY—Homostimulation is the most valuable single prospect in organotherapy. By it, functionally inactive or deficient glands may be persuaded to resume their normal work. The hormones have a definite stimulative and restorative action on the glands corresponding to those from which they are made. This postulate was first stated by L. Hallion, of Paris (*Presse méd.*, 1912, xx, p. 433), in what has come to be called Hallion's law:

"Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration."

Although this theory has been subjected to critical investigation, it is now quite generally accepted. Physiologists and conservatives alike recognize its integrity and value. For example, R. G. Hoskins for long the editor of *Endocrinology,* believes that "there is some definite evidence in its support." In "Endocrinology and Metabolism" (Vol. I, p. 15), he states:

"In some instances the effects of administering endocrine gland substances by grafting or otherwise seem to be due, in part at least, to the stimulation of latent cells by the corresponding organs. For example, a case has been described by Morris (1916) in which a testicular graft was implanted to compensate for atrophy of the gonads. The procedure resulted in marked development of the atrophic testes which had been left in situ."

Here, then, is one of the fundamentals of this method of treatment. While it is manifestly futile to hope to regenerate an organ that is totally destroyed, it has been proved possible again and again to reinvigorate that part of the

gland which is not yet beyond the hormone stimuli, and even to cause a hypertrophy sufficient to restore a measure of the organ's former usefulness. But the idea of homostimulation is not yet fully accepted. For instance, in June, 1931, L. G. Rowntree, of the Mayo Clinic, emphatically states that "no gland can be stimulated to activity by its own product." (Discussion in *Jour. Am. Med. Assn.*, Aug. 22, 1931, xcvii, p. 522.)

Typical examples of this therapy are the use of thyroid extract in simple goitre (57), and more especially in functional hypothyroidism (67), and of ovarian preparations in functional dysovarism (80).

SYMPTOMATIC OR SPECIFIC ORGANOTHERAPY—A number of the glandular extracts are used for their specific pharmacological actions. This is the one organotherapeutic method about which there is no disagreement. Adrenalin and pituitrin are in common use as drugs. They are not used ordinarily either to correct an underlying cause, to restore physiological action, or to replace missing secretions. We know perfectly well that asthma and shock are not manifestations of a lack of epinephrine, and that the muscular atonia in delayed labor or intestinal paresis is not due to posterior pituitary insufficiency. The value of these products lies in their remarkably potent and specific pharmacodynamic or drug action.

EMPIRICAL ORGANOTHERAPY—There are still some products in regular use for which there is no scientific justification; yet the patients seem to improve by their use, and that is more important to them than anything else. Some conditions of unknown etiology and pathology respond to organotherapy sufficiently to maintain the confidence of some physicians in a given remedy, and this being so they are as well justified as those who would let the patient suffer rather than use an empirical method. An illustration of this is the use of parathyroid in certain types of arthritis (38), or of Splenocrin* in dermatoses associated with eosinophilia (21).

ENDOCRINE CATALYSIS—More than ten years ago, James M. Wilson, of Philadelphia, made the verbal suggestion that the sudden responses to organotherapy and the astonishing results that sometimes come from very small doses may be explained best on the basis of catalytic action. Since then the idea has become quite generally accepted, and we are no longer so surprised at the spectacular results we sometimes obtain.

The illustration of the pendulum has often been used—a push, and it starts, but it does not swing long unless there is a motive force. The response that the endocrine principle is able to produce is limited by the inherent capacity of the patient's glands to respond to the stimulation.

CLINICAL IMPROVEMENT A TRUE CRITERION—The philosophy of considering a patient from the endocrine standpoint is suggested as a means of broadening our present therapeutic knowledge of diseases that certainly are not in the current lists of endocrine disorders—neurasthenia, rheumatism, acidosis, epilepsy, chronic ulcerations, dermatoses, to mention only a few. If a patient comes with a complaint of this nature that has not responded to other treatment and we discover an incidental endocrine symptom *and treat it,* many times we will find to our surprise that there is improvement in the original disturbance.

Frequently the difficulty of a given symptom-complex is solved only by applying our knowledge of the endocrine functions and their regulation by adding organotherapy to the other indicated measures. This often enables us to extend both our knowledge of the patient's ailment and our means of controlling it. It is unscientific and reprehensible to some, because "one cannot tell which part of the treatment is responsible for the improvement that may follow"—as though the sole aim of therapy were to determine the value of a remedy! What should we care about the credit earned by a remedy, so long as we help the patient more thoroughly, more quickly, and more conveniently than without it?

In no sense does this mean that we should stifle the desire to establish scientifically every therapeutic measure that we employ. Relentless pursuit of this ideal is the soul of sound therapy. But if, while we search, the patient were to be denied a remedy that has the insistent testimony of wide clinical efficacy, he might suffer because of our ignorance. Before we abandon any empirical treatment, we should answer the question, "Does it add to the service we are able to render the patient?"

When the affirmative answer to this question is analyzed, most of it is found to be a record of the patient's subjective feelings; earlier, it is true, the tendency has been to discount these expressions. But coincidence cannot happen many times without becoming conviction, and this conviction is strengthened the more as the euphoria is found to be a part of a picture that includes clinical and laboratory changes that are capable of fairly accurate measurement.

A patient feels better, and a blood-pressure of, say, 80/55 is found to have raised to 115/70 within a week or two following adrenal support. Another patient looks better following certain liver therapy, and the blood-count shows an improvement of, say, a million red cells in ten days, perhaps after a month of less obvious response to what had been thought to be the proper treatment. Again, an ovarian irregularity of years' standing is not only nor-

malized from the standpoint of the amount, character, and particularly the regularity of the flow, but the patient loses twenty pounds in weight, and the basal metabolic estimation shows an increase of twenty points!

Are not the feelings of the patient often as clinically valuable as the other findings? In no case can we wholly discount them. A good laboratory report is cold comfort to a patient whose symptoms remain unchanged, and the doctor can repeat such reports until he is blue in the face, but they will not help his patient much if unaccompanied by controlled symptoms and changed feelings. We rightly tend to discount the patient's opinion of his own progress, but now there is danger that we may swing to the opposite extreme. It is surely better therapeutics to have a patient believing in his improvement, real or fancied, than to have to try to convince him by laboratory reports against his own feelings. The successful physician is the one who knows best *how to make his patients feel better*. Subjective improvement following indicated organo therapy has very often surprised a physician into an admission regarding this form of therapy that he has previously hesitated to make.

As an example of this, let me relate a recent experience of a physician who with three associates, is specializing in the treatment of colon and rectal diseases. Having discovered the muscular influence of Adreno-Cortin,* the adrenal cortex hormone, they used it in a few of their usual run of cases. Soon these doctors were using Adreno-Cortin as a routine, so a colleague asked for information, to which they replied:

"Before answering your question regarding Adreno-Cortin, allow me to make a few brief statements. The patients received into this Clinic are chronic cases that have passed through the hands of one or more doctors and sometimes as many clinics.

"Prior to treatment each patient receives a physical examination including a check-up of the endocrine glands, blood-count, B.M.R. test, occasionally a polygraph tracing, blood-pressure reading which includes pressure-phase analysis, fluoroscopic examination of the chest, X-ray of the colon following a rectal injection of barium with buttermilk, and the usual rectal and sigmoid examination. . . .

"First, I would state that all cases received by the Clinic indicate hypoadrenia to a greater or less degree (fatigue syndrome, asthenia, hypotension, Sergent's line, etc.). Approximately 80 per cent. are hypothyroid. Secondary anemia appears in practically all cases, and approximately 50 per cent. show indicanuria.

"In regard to our treatment of hypoadrenia, . . . Adreno-Cortin in capsules is being used, 1, t.i.d. at meals, with uniformly good results. In obstinate cases we also use Adreno-Cortin, 1 cc. intramuscularly, repeated every two or three days until five or six injections have been given."

In a personal communication, it was disclosed that such attention to the

adrenal aspect of colon and rectal cases made these patients "feel better sooner." The reason will be found in the consideration of the treatment of colitis (53).

OPPOSITION TO ORGANOTHERAPY—"Why has there been so much said against organotherapy?" asks one. An answer to this would take a lot of space, and when it was completed we should have learned nothing useful. When, however, one is asked why so much has been published in defense of organotherapy, the answer is: *It has revolutionized our conceptions as well as our treatment of scores of problems in every phase of medicine.* These changes are not just improvements, advances, or amendments, but a radical recasting of our whole conception of certain diseases and a complete rehabilitation of our ideas of the etiology, diagnosis, therapy, and prognosis of many a disease.

How ridiculous would be our position if we were forced to consider cretinism from the point of view obtaining before George R. Murray, then of Newcastle-on-Tyne, suggested thyroid feeding in 1891! How handicapped our control of diabetic coma if insulin were unknown! How different the prospect in delayed labor, the crisis of asthma, shock, or pernicious anemia, if the advances in organotherapy were denied us!

The "promised land of endocrinology" has been opened to our astonished gaze. Step by step we are entering in to possess its bounties.

Listen to a few of these superlatives: First, from an editorial in the *Lancet* (April 28, 1928, cciv, p. 863), referring to the new treatment of pernicious anemia:

"Two years ago there would have been few medical men credulous enough to believe in the possibility of so simple and yet so specific a cure for a hopeless condition. . . . This ranks as one of the most sensational episodes in the history of medicine."

Again, the editor of the *Journal of the American Medical Association* (Jan. 24, 1931, xcvi, p. 273), in commenting on the experiences of Rowntree and his associates with an adrenal cortex hormone, says:

"One may confidently expect that, to the successful clinical use of insulin and liver extract under conditions in which, without them, death would be impending, may soon be added the relief of the dire Addison's disease by the cortical hormone."

An editorial writer in *Endocrinology* (Sept.-Nov., 1923, vii, p. 727), while paying just tribute to the discoverers of insulin, visualizes just what had materialized since 1921:

"The isolation by Banting and coworkers of the specific hormone of the islands of Langerhans, and its clinical application to the treatment of diabetes

mellitus, is universally acknowledged to be one of the most brilliant achievements in medical science and therapeutics. Their steadfast persistence in the face of many obstacles and despite the discouraging failures of previous workers, merits unstinted praise and congratulation. . . .

"What a heartening stimulus to the future, what a broad significance therefore attaches to the achievement of insulin! If the true specific hormone of the islands of Langerhans can be isolated, what is to prevent a similar accomplishment for the anterior lobe of the hypophysis, the ovaries, testicles, and adrenal cortex? Indeed, there are lights on the horizon already, and a new dawn for endocrinology and humanity seems assured."

Since this was written, potent principles have been perfected from "the anterior lobe of the hypophysis, the ovaries, testicles, and adrenal cortex," all of which are clinically meritorious and the character and potency of which are proved by experiment in the physiological laboratory. Accretin* (18) is the growth hormone; Plestrin* and Lydin* (11) are the female and male sex hormones, respectively; and Adreno-Cortin* (9) is the cortical hormone, capable of maintaining life in bilaterally adrenalectomized animals.

HOW SHALL WE MEASURE DOSAGE?—Endocrine therapy is being used by tens of thousands of physicians, and many of them have acquired the trick of giving it with maximum advantage and convenience to their patients. Since success from the administration of organotherapy depends upon (1) the accuracy of the diagnosis, (2) the size of the dose, (3) the response of the patient, and (4) the time that treatment is continued, it is obvious that the measurement of the dosage depends upon circumstances that vary with each patient. These factors are so inconstant that it is almost impossible to measure them; the weather, the digestion, the emotions, and the normal processes and circumstances of life change them from minute to minute.

Endocrine therapy, then, must be applied by the empirical method. My thyroid function test (31) is a convenient procedure based on this very idea. The patient's response is our best guide. From an experience extending back for forty years, it is known that certain dose figures are the averages, but that endocrine responses vary greatly and the right dose for one patient is wrong for another.

It is intended later to make clear that many failures obtained in spite of carefully estimated doses of a necessary extract may be avoided by simultaneously treating the other glands as well. The basis for such pluriglandular therapy is the salient, fundamental principle of medical practice—treating the patient rather than his disease.

Step-ladder dosage is sound policy. Consider the case from the various

endocrine angles, treat the picture as it appears to you, then supplement this "background" pluriglandular therapy by gradually increased doses of the product appropriate to the main dyscrinism. This enables one to render a greater service than otherwise, and gives an idea of the patient's tolerance, which renders the diagnosis more accurate.

THE PLURIGLANDULAR IDEA—If the philosophy of the glandular balance is sound, we must have a corresponding therapeutics. If an endocrine defect causes endocrine stress elsewhere, we must add to the measures calculated to modify the original defect, those directed at the reaction as well.

The menopause is the best illustration of this: The ovarian insufficiency of the climacteric is normal and expected; it is the resulting concern on the part of the thyroid and the pituitary that causes the abnormal reactions. The thyroid is played out (90 per cent. of all cases of myxedema are found in women, and 95 per cent. of these occur between the ages of forty and fifty); the pituitary takes on a greater load than that to which it is accustomed (pituitary headache is a real problem at this period, and much of the obesity of midlife is pituitary in origin); balance is destroyed, resulting in the usual circulatory upsets and fatigue syndromes.

The ovarian treatment of the hypovarism is not so much an attempt to reestablish the ovarian functions as *to lessen the need for concern by the other glands;* and the thyroid and pituitary products, now so commonly added to ovarian therapy, are directed at the really abnormal features of "the critical age," which will be fully considered later (80).

Another phase of this idea may be emphasized: A case that requires endocrine therapy usually has two aspects to be considered: the major dyscrinism, which is the real shortcoming; and the associated dyscrinism, which is the reaction to it. For reasons already explained, it is preferable to treat all the patient's difficulties rather than only his most apparent one. So there must be two complementary efforts: (1) to modify the endocrine background as best one can, and (2) to make up for the real and outstanding shortcoming. Pluriglandular therapy, therefore, is particularly suitable for obesity in women, the neurocirculatory imbalance at the menopause, and the developmentally defective child—*because it lessens the stress upon the upset endocrines* so that they are better able to respond to the treatment.

After doing this as well as we can, we proceed to treat the principal endocrine disorder—pituitary, adrenal, or thyroid, as the case may be. Then, later, when the other has been continued for several days or weeks, we intensify the uniglandular therapy and get the best response by proceeding in step-ladder fashion.

This is the opposite of the more usual method, which starts with the obvious disorder and gradually broadens the treatment as indicated by the poverty of the patient's response. For example, in hypothyroidism the wavering thyroid mechanism might reasonably be expected to give a better response if we have cleared the way by lessening the pituitary or ovarian demands upon it. So I advise pluriglandular therapy *first* with every appropriate associated measure, then later I suggest the more direct and aggressive treatment of the main dyscrinism.

In one of his special Endocrine Issues (110), the editor of the *Prescriber* (Oct., 1923, xvii, p. 374) considers the subject, "Pluriglandular Therapy," and relieves himself of the following remarks:

"Treatment by means of combinations of glands is anathema to the conservative pharmacologist; it seems to him to have no place in scientific medication. On the other hand, it is the main plank in the platform of the manufacturer of glandular products. . . . The mere fact that pluriglandular preparations have proved a sound commercial proposition proves beyond question that this form of medication is popular with the profession, for these products as a rule are not sold except on prescription. One is led to ask, then, why this extreme popularity, if the leaders of endocrinological thought do not approve? There can be only one answer—results. . . . We hold no brief for the manufacturers, but we see no reason why a preparation should be condemned simply because it is manufactured and sold commercially. The line between science and commerce is very difficult to draw: Science is rapidly becoming commercialized and commerce is being more and more directed in a scientific or professional spirit. The most successful manufacturers of glandular products . . . employ highly trained scientists to elaborate and test their products; they have literary departments which would put to shame the editorial resources of some of our scientific journals; above all, they seem to make their first principle one of service to the profession and through them to the patient. . . .

"The real question is: Is pluriglandular therapy justifiable? We know that most endocrine syndromes are pluriglandular, but we cannot in every case say exactly which glands are out of order. . . . If we could—and there are cases when we can—the true scientific method would be to write a prescription for the glands required. . . . When exact diagnosis is impossible, as it is in the vast majority of cases, one must fall back on empiricism, and in the pluriglandular products of the more reputable houses we can have our requirements met in a manner which has given, and doubtless will continue to give, the results looked for."

PROTECTING EXTRACTS FROM DIGESTION—It is well known that certain endocrine principles are most effective when given parenterally: Adrenalin for its effect in asthma, pituitrin for its oxytocic effect, and insulin in diabetes, practically always are given by intramuscular injection. Much misunderstanding and many misstatements have arisen from this.

Parenteral organotherapy is usually given for a purely pharmacodynamic effect, *i.e.*, from the principle itself, direct. Oral organotherapy is usually given for an endocrine or homostimulative effect which does not usually produce an immediate or spectacular response, but results in a reeducation of the patient's own depleted glands, with gradual reestablishment of their functions and a coincidental restoration of the balance between the defective glands and their intimate associates. This always takes time, and, although injections are not without value in this respect, tablets or capsules are certainly much more convenient for the patient who requires long-continued organotherapy.

The "destroyed-in-the-stomach-with-the-exception-of-thyroid" idea has been aggressively reiterated, but is now as little supported by fact as formerly by theory. Why should thyroid extract alone be immune to destruction by digestion, and why should it be the only hormone-containing extract to reach the blood in acceptable form? Why does not the tryptic digestion, which is known to go on in the blood stream, destroy the numerous endocrine principles carried therein? How does the parathyroid active principle survive its separation from its original source by boiling with hydrochloric acid, or secretin its extraction from the duodenal mucosa by hydrochloric acid?

Endocrine extracts do in fact have to be digested before their active principles can be separated and assimilated by the intestines, and to interfere with this digestion is absurd. Whether the digestion takes place in the stomach or in the intestine is immaterial. Persons who have *achylia gastrica* and serious malassimilation may actually fail to respond to organotherapy in proportion to the defective digestion of the glandular extracts. This difficulty can be overcome by giving the products with the food, hydrochloric acid and perhaps other digestants being given also. The proportion of such failures will be reduced, and enteric-coated products will not be found in the stools.

Any physician can easily test the comparative efficacy of thyroid therapy as it is usually prescribed and thyroid in enteric-coated form. Prescribe the latter in several cases known to need thyroid in definite amounts. Continue the treatment for some days, then suddenly replace the coated product with the same dosage of a potent, unprotected tablet. In three out of four cases the patients will complain of thyroidism, just as they invariably do when a thyroid product dosed on a fresh substance basis (as the Burroughs Wellcome & Co. tabloids) is replaced by a product dosed on a dry gland basis (as the products of Armour or Parke, Davis & Co. or any U.S.P. thyroid extract).

In speaking of adrenal organotherapy in hypoadrenia, C. F. Arroyo, of Tampa, Florida (*Med. Jour. and Rec.*, Jan. 2, 1924, cxix, p. 25), says:

"The treatment of hypoadrenia should tend, first, to remove the cause of the condition if possible . . . the entire organ should be used. . . . The objection that, in giving the gland by mouth, the hormones may be destroyed, cannot be admitted because . . . they are absorbed and eliminated without change after the catalytic action has been exerted."

Further, Ivo Geikie Cobb, of London ("Aids to Organotherapy," New York, William Wood & Company, 1922, p. 11), confirms oral administration when he says:

"Oral administration of the bodily hormones is in wide and general use; indeed, it may be said that this is the most usual method of exhibiting these substances."

As the reader will see further along, scores of physicians whose work has enabled us to advance in this field and whose opinions are collated here, have built their successes upon experiences with glandular *feeding*—not only with thyroid, but with many analogous products such as liver extract, which has spectacular effects on blood regeneration; pituitary substance, which controls the fierce pituitary headache; or ovarian extract, which William P. Graves, of Harvard University, considers a "near-specific" in menopausal difficulties.

WHAT IS "A FAIR TRIAL"?—A common phrase in my correspondence is "a fair trial"; and apparently there are very wide differences of opinion as to what this really means. Too many physicians seem to judge organotherapy as they would a cathartic or an analgesic drug.

Neither a single case nor yet a dozen cases of long-standing chronic disease are enough to demonstrate the value of endocrine therapy; but many a physician, using organotherapy for the first time in the treatment of a given complex is willing to pass judgment on the remedy and even on the method in that single case. Though the outcome may have been "better than could be expected," it is wrong to decide from one experience that the method is fundamentally good, for the organotherapy is but a part of the entire treatment, and the benefit may not really be due to it, despite the fact that "improvement did not seem to begin until we started in with ——."

Not only has organotherapy been judged many times by its apparent effects in too limited a series of cases, but it has been more seriously misjudged by the results following its use for too short a time. Time and again there has been criticism because a certain suggested product failed to produce the expected results within a few weeks, when perhaps only a hundred tablets had been given. If what has been termed "the educative character" of the influence of organotherapy were better understood, this would not occur.

7. AN HYPOTHESIS OF HORMONE HUNGER

WHEN THE blood plasma is considered as a humoral channel through which the endocrine principles are carried from one part of the body to another, it is not surprising to find oneself wondering at the extent and complexity of the mixture. The blood is, among other things, a pluriglandular solution. When we try to explain how a given substance, mixed with so many other similar substances, can be separated and utilized by a specific tissue, there emerges the principle of cell selectivity, one of the fundamental principles of biochemistry, whereby each tissue possesses a well-developed faculty of appropriating the kind and amount of hormones that are required; and that faculty in turn depends upon hormone stimuli for its physiological regulation.

While attempting to understand some empirical findings, the author hit on what has been called the "hypothesis of hormone hunger." This idea was first published in the *New York Medical Record* (Aug. 16, 1919, xcvi, p. 276) as an explanation of what undoubtedly happens but cannot be proved.

Not a few clinical experiences with various forms of organotherapy in endocrine disturbances have convinced me that there are varying degrees of receptiveness to hormone stimuli on the part of various individuals. In other words, sometimes a very rapid and remarkable result may be obtained; at other times, in seemingly similar cases, the reactivity of the patient differs, and the results are not so good nor so rapid.

Each organ of the body that is dependent upon hormone influences must have some subtle capacity to pick up the hormones from the blood as they float by. This cannot but be true, else how could the passing chemical messengers bring about the influence on the organ or cell that they affect? Not only must there be a definite capacity to pick up these hormones as they are brought to the cell by the blood, but there must be a selective capacity, for the blood contains all the hormones that we know of and probably a good many more that we do not know about at present. The imagination does not have to be stretched very much to conceive of a remarkable cellular judgment or selective capacity to choose the hormones that are needed, and in the amount that they are needed.

With this particular selective power in mind, I have developed this hypothesis of hormone hunger. Under varying circumstances these cells must be more active in their picking up of the passing hormones than at other times. In other words, a condition of hormone hunger must actually be present at times. To explain: consider the thyro-ovarian interrelationship, which is, perhaps, the most thoroughly established and most easily understood. It is recognized that the thyroid principle exerts a marked influence on ovarian function. (It will be recalled that there are definite functional ovarian disorders in myxedema, that girls with goitre very often have serious menstrual difficulties, and, finally, that the cretin, who has no thyroid gland, does not develop sexually.) Surely it is fair to believe that there is a principle made

in the thyroid which stimulates ovarian function; and that this must necessarily reach the ovaries through the blood; and, of course, that the ovaries must have some means of getting hold of this hormone. If, then, this thyroid hormone, passing through the ovaries in their blood supply, happens to be deficient, and the demand is greater than the supply, there will remain a need for that which is not present, *i.e.*, the ovarian cells will be "hungry" for the thyroid stimulus. Further, the degree of this hunger will vary, depending upon the thyroid function and the hormone needs of the ovary.

In a case of well-defined hypothyroidism it is reasonable to suppose that the ovarian cells are getting along as best they can with little or none of their usual stimuli (and right here enters the fascinating study of the effects of hormone hunger on other endocrine glands—how the pituitary, for instance, may function faster to make up for deficiencies in its associates, etc.). If we attempt, by means of organotherapy, to modify the clinical disturbances that result from this hormone insufficiency, the application of this hypothesis enables us to appreciate that the hormone hunger of these ovarian cells increases their presumed "urge" to pick out from the circulation the additional hormones that we may give by mouth and, incidentally, to benefit from the enhanced hormone production that follows organotherapy (homostimulation). This selective capacity is in proportion to the cellular need.

To put it another way: If we give thyroid extract as a therapeutic measure in dysovarism, the ovaries are unusually interested in securing the thyroid hormone from the blood and they will select it with greater or less avidity, depending upon the degree of hormone hunger that may be present. Likewise, as soon as the needs of these glands have been satisfied, the unusual facility with which the hormones are chosen from the blood stream will cease to manifest itself. We presume that superfluous amounts of any or all the hormones will remain in the blood until they are either used or finally oxidized.

There is another important phase of this matter that seems to be explained more satisfactorily by this hypothesis than in any other way. We are convinced that the intimate interrelationships of the glands of internal secretion practically eliminate the possibility of endocrine disturbances involving a single endocrine gland. That is to say, where there is a disturbance of one internal secretory organ, there immediately develops an associated functional derangement of the hormone balance, involving one or more of the glands most intimately dependent upon the gland originally affected. Hence pluriglandular disturbances are the rule, and, therefore, pluriglandular therapy must take the place of the most obviously needed glandular extract.

To illustrate: The cretin is in dire need of the physiological stimulation of the thyroid hormones. Many times a cretin develops remarkably on thyroid alone, and then seems to reach a barrier beyond which no progress is made. If, then, extracts of the associated glands, especially the anterior pituitary, are given *with the thyroid,* progress is resumed and sometimes far exceeds that previously made. This applies with equal force in many other pluriglandular dystrophies, the most common of which is the thyro-ovarian dysfunction already mentioned.

This hypothesis of hormone hunger explains the "how" of pluriglandular therapy. Many times I have wished that it were possible to determine the degree of glandular insufficiency in a given individual, just as we can estimate the urinary solids and differentiate the percentages of urea, chlorides, phosphates, etc., or the differential blood-count. It would be ideal to be able to establish that, for example, a given case is 50 per cent. low on thyroid, 35 per cent. low on ovarian, and 20 per cent. low on pituitary hormone functioning! Obviously this would facilitate a definite therapeutic recommendation; but it cannot be done. However, based on the hypothetical principle of hormone hunger, we can offer a pluriglandular mixture and *let the body do its own selecting.*

We can trust the organism to pick out from the menu that we offer it, those hormones that are needed most and in the degree needed. Then, based on the previously mentioned condition that might be called "hormone satiety," the limited excess of unused hormones floats on until used or destroyed. This explains the reason for the clinical experiences that many may have had with the same pluriglandular therapy in several somewhat dissimilar cases.

It seems that this hypothesis is well founded, is based on sound reasoning, and is at least worthy of consideration. To me, it explains many things that I have repeatedly seen in clinical organotherapy. At all events, the selective capacity of the cells cannot be gainsaid; and the clinical results are certain, whether the hypothesis is true or not.

Time has maintained this hypothesis unimpaired, though the fact is recognized that excessive amounts of the thyroid hormone, whether produced in the body or administered therapeutically, will be appropriated to the detriment of the organism. The hypothesis, however, was based on a concentration or dosage of endocrines *within normal limits.* One can give certain drugs with advantage provided the dosage is right, but beyond these reasonable amounts they become detrimental poisons.

The reader is reminded that the principle of cell selectivity is a well-established one. The bone cells have a faculty of appropriating calcium that muscle cells do not, and have varying degrees of calcium hunger depending upon age and other circumstances. The thyroid cells are the only cells in the body known to utilize iodine—evidently they have a peculiar faculty for appropriating this element. The liver is capable of separating certain substances, both food and toxin, from the blood that passes through it, storing up the glycogen and metamorphosing the waste into products suitable for elimination.

This hypothesis of hormone hunger seems to me to give a reasonable explanation of the mechanics of endocrine function and organotherapy.

II

THE ENDOCRINE PRINCIPLES

8. INTRODUCTION

WE HAVE seen that the essence of endocrinology lies in the fact that the endocrine organs manufacture active chemical principles which in health and disease are produced in normality and abnormality, respectively, thereby bringing about, or failing to bring about, certain vital physical and chemical reactions in various parts of the organism. These substances are necessary for a healthy functioning of the organism, and in ill-health the body attempts either to produce them in excess or to stimulate the secretion of their synergists to compensate for the functional inadequacy.

We have seen that these hormones are definite chemical substances of such a nature that they may be isolated, separated, or concentrated into a form that makes it possible to use them to replace or supplement the corresponding principles that may be lacking in the patient's organism.

We have seen that the discovery of the hormones as a whole and their individual perfection have disclosed to the profession a series of therapeutic agents that have completely recast many of our conceptions of physiology and have revolutionized our prospects in therapeutics. A great field has been opened up which naturally divides itself into the experimental research in biochemistry and the clinical evaluation of its results.

In this section we shall consider the endocrine organs as sources of remedial agents and a number of the numerous endocrine products now at our disposal.

There has been a gradual change in the therapeutic use of the active principles as the methods of isolation have been perfected. When thyroid therapy was initiated about forty years ago, the feeding of thyroid sandwiches was in vogue. A few years ago liver feeding reached a point where calves' liver became an expensive luxury. The introduction of vacuum-dried desiccations about thirty years ago was a great advance. Defatting processes were then perfected which rendered the products much more stable, these "extracts" lending themselves to convenient dispensing in tablet or capsule form. As time went on it was found possible to remove more completely the inert cellular

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THE ENDOCRINE GLANDS: THEIR PRODUCTS, PHYSIOLOGY, AND THERAPY

(A table based largely on that of Prof. E. Gley, of Paris)

Character	*Organ*	*Product*	*Rôle*	*Relations*	*Diseases*
A. NUTRITIONAL AND TROPHIC SUBSTANCES	(a) Adrenals (Medulla)	Epinephrine	Sugar Mobilization, Sympathetic Stim.	Adrenals, Pancreas, Liver	Hyperadrenia, Hypoadrenia (Addisonism)
1. Substances Assisting Nutrition	(b) Liver	Glycogen Hemopoietin	Energy (muscular) Hemopoiesis	Liver, Muscles Liver, B. Medulla,	Hepatic Diabetes (?) Anemia (especially pernicious)
	(c) Pancreas	Insulin Trypsin	Glycolysis, CH utilization, Digestion	Pancreas, Adrenals Liver, Pancreas, Duodenum	Diabetes Mellitus, Pancreatic Indigestion, etc.
	(d) Pituitary (Post. Lobe)	Infundin	CH metabolism		Obesity
2. Detoxicative Regulators	(a) Liver	Anabolin	Detoxication, Ureagenesis	Liver, Thyroid, Parathyroids	Hypertension (func.), Toxemia (hepatic)
	(b) Parathyroids	Parathyrin	Detoxication, Calcium Fixation	Liver, Thyroid	Hypocalcemia, Tetany, Hemophilia, Spasmophilia, etc.
	(c) Thyroid	Thyroxin	Regulation of Metabolism and Detoxication	Thyroid, Parathyroids, Liver	Hypothyroidism, Cellular Infiltration, Obesity, Hyperthyroidism
3. Morphogenic Stimulants	(a) Gonads (M) (Leydig Cells)	Lydin	Development, Growth, Secondary Sex Char.	Testes, Thyroid, Pituitary, Thymus	Infantilism, Eunuchoidism, Asexualism, Aspermia
	(b) Gonads (F) (Ovaries, C. Lutea)	Lutein Folliculin	Reproduction	Ovaries, Thyroid, Pituitary, Thymus	Infantilism, Amenorrhea, Asexualism, Sterility
	(c) Thyroid	Thyroglobulin (?)	Development of Gonads, Bones, etc.	Gonads, Pituitary, Thymus, Bones	Hypoplasia, Developmental Defects

	(d) Pituitary (Ant. Lobe)	Tethelin Accretin Apestrin	Development of Gonads, Bones, etc.	Thyroid, Gonads, Bones	Dwarfism, Acromegaly, Acromicria, Hypogonadism
B. FUNCTIONAL ENDOCRINE STIMULANTS	(a) Liver	Antithrombin	Blood Coagulation	Liver, Parathyroids, Spleen (?)	Hemophilia, Purpura
	(b) Duodenum	Secretin	Pancreato-Biliary Stimulant	Duodenum, Pancreas	Indigestion, Pancreatic Insufficiency, etc.
		Cholecystokinin	Gall-Bladder Evacuant	Liver, Gall-Bladder	
	(c) Adrenals (Cortex)	Adreno-Cortin	Muscular Chemistry and Tone	Adrenals, Muscles, Heart, etc.	Addison's Disease, Asthenia, Hypotension
	(d) Placenta	Placentin (?)	Galactagogue, Uterine Involutant	Placenta, Uterus, Mammæ	Agalactia, Uterine Subinvolution
		Plestrin	Estrus Stim., Gonadotrophic	Uterus, Ovaries	Sterility, Hypoplasia
		Plagonin	Activates Sex Hormones	Gonads, Pituitary (Anterior)	Asexualism
	(e) Thyroid		Deaminization	Liver, Cellular Tissues	Malnutrition, Acidosis
	(f) Pituitary (Post. Lobe)	Hypophysin	Musculotonic, Fat and CH Metabolism	Pituitary (Post.), Pancreas, Thyroid	Obesity, Diabetes Insipidus
C. MORPHOGENIC ENDOCRINE ROLE (Still questioned)	(a) Spleen	Colloidogenin	Mineral Control	Spleen, Parathyroids, Liver	Hypocalcemia, Tuberculosis, etc.
		Splenocrin	Antagonizes Eosinophilia (?)	(?)	Certain Dermatoses
	(b) Thymus	Thymocrin (?)	Development	Thymus, Gonads, Bones	Defective Development —physical, mental
	(c) Mammæ	Mammin (?)	Anti-Ovarian, Galactagogue	Mammæ, Uterus, Ovaries	Hyperovarism, Menorrhagia, Agalactia
	(d) Pineal	Epiphysin (?)	(Not Proved)	Brain, Pineal, Gonads	Precocious Puberty (?)
	(e) Prostate	Prostin (?)	Gonad Cooperative	Prostate, Testes, Thyroid	Hypogonadism, Prostatic Hypertrophy

material, leaving only the concentrated substance that contains the active principles in powder or solution, as the case might be.

A series of hormones were thus separated and made available, usually by fractional solvent methods. These "fractions" have been studied, standardized, and used with maximum conviction of their potency, stability, and therapeutic prospects. Some indeed have been obtained in crystalline form.

This last step of crystallization, although of decided chemical interest, has not been more of an advance than the previous ones, for in several instances the product has been "too perfect." For instance, thyroxin does not represent all the therapeutically active material in thyroid extract, nor does theelin offer any clinical advantage over folliculin and estrin, the concentrates of equal standard.

Another step has already been taken with three products—thyroxin, the adrenal medullary hormone, and the pancreatic hormone, which have been synthesized from material quite remote from the endocrine tissues from which their original counterparts were separated. These synthetic endocrines are not yet in general use because the technical methods are more expensive than those involving the use of animal glands—the production of synthetic epinephrine costs considerably more than that of adrenalin—and the ultimate products seem to vary somewhat in their clinical effects; synthetic insulin, for example, is too harsh.

In the following pages each gland is considered separately, and each preparation is discussed from the standpoint of the physician rather than that of the research worker. Many names of glandular preparations are omitted, for there is a multiplicity of names for each active principle based upon individual, geographic, and business considerations.

The accompanying table, originally translated from a publication by Eugen Gley, of Paris, and published in the book, "Endocrine Diagnostic Charts" (1929), has been edited and brought more nearly up to date. It is intended to give a fairly comprehensive survey of the subject.

NOTE: At the close of each of the succeeding chapters in this section will be found a list of several endocrine products and active principles. Not all of these are available for therapeutic use, so, to differentiate these substances, they are divided into three classes:

1. Available remedies — practically all names listed are trade names. This class is subdivided into (1A) physiologically standardized active endocrine principles, and (1B) glandular extracts.

2. Active principles and extracts of technical and experimental interest, some of which are standardized while others are not.

3. Active principles postulated but not isolated.

Throughout, the asterisk (*) indicates products with whose development I have had to do personally, and that are supplied by The Harrower Laboratory.

9. THE ADRENALS

The Medullary Hormone—Standardization—The Cortical Hormone—Standardization—Adrenal Products, Medulla and Cortex.

THE ADRENAL glands, also called the suprarenal capsules, were discovered by Eustachius between 1550 and 1560. They are small pads of tissue of a reddish-brown color, lying above and in front of each kidney. In man, each adrenal normally weighs approximately 2 Gm. The anatomy and physiology of these glands are complex, so much so that within the last decade many vociferous differences of opinion have been recorded in the medical literature.

The adrenals are divided into two parts, the cortex (about 85 per cent.) and the medulla (15 per cent.). These arise from different embryological structures, and differ histologically and functionally. The former is the more vital to the body, while from the latter is produced one of the most potent endocrine principles known—adrenalin, the first hormone remedy.

One of the outstanding clinical accomplishments in a century of medicine was the observation of Thomas Addison, of London, that connected the asthenic syndrome that bears his name with adrenal destruction (35). Another equally important advance was the discovery in 1894 by G. Oliver and E. S. Schafer, of Edinburgh, of the pressor influence of the medullary portion of the glands. Of the same epoch-making character have been the perfection during the last few years of the cortical hormone and the clinical discoveries connected with its use in medicine.

THE MEDULLARY HORMONE—An early finding concerning the reactions of epinephrine, prior to its isolation, was demonstrated in 1856 by G. Colin, of Paris ("Traité de physiologie comparée," Paris, 1856, p. 483), who showed the development of a blue color when ferric sulphate was applied to the cut surfaces of the glands. A. Vulpian, also of Paris (*Compt. rend. Acad. d. sc.*, 1856, xliii, p. 663), was the first to present proof of the internal secretory character of the medulla. He treated the tissue with ferric chloride, and the emerald green color obtained was changed to red on the addition of dilute alkali. This color showed in the adrenal vein also, convincing him that the medullary secretion passes into the blood stream. The brownish color developed with chromic acid was discovered by J. Henle, of Göttingen (*Ztschr. f. rat. Med.*, 1865, xxiv, p. 143), who suggested the term "chromaffin tissue" for the adrenal medulla.

Apparently the first extract was prepared in 1867 by F. Holm (*Jour. f. prakt. Chem.*, 1867, c, p. 150). He also discovered some of the basic principles of the chemistry of epinephrine. He extracted with dilute alcohol,

dissolved the residue in water, and precipitated the proteins with basic lead acetate. After removal of the excess lead with hydrogen sulphide, the epinephrine was precipitated with ammonia.

It was almost thirty years afterwards (1894) that the fundamental experiments of G. Oliver and E. S. Schafer, of the University of Edinburgh (*Jour. Physiol.*, 1894, xvi, p. 1; 1895, xvii, p. 9; and 1896, xviii, p. 230), gave us our early working knowledge of this subject. They prepared extracts with many solvents, including water, glycerin, alcohol, and ether. Such extracts, when effective, were capable of causing a brief rise in blood-pressure when injected into animals. Absolute alcohol and ether did not extract the pressor substance. They further showed that the medullary tissue was the source of the active material.

Following these preliminary studies, O. von Fürth, of Leipzig (*Ztschr. f. physiol. Chem.*, 1897, xxiv, p. 142; 1898, xxvi, p. 15; 1900, xxix, p. 105), and J. J. Abel, of Baltimore (*Bull. Johns Hopkins Hosp.*, 1898, ix, p. 215; 1901, xii, p. 80), were the first to relate attempts at the isolation of the pressor substance. Abel extracted ox adrenals with dilute acid and, by the addition of benzoyl chloride, formed a benzoyl derivative. Acid hydrolysis resulted in the formation of a salt of the base, which was active but probably impure. From his analyses Abel drew the wrong conclusions as to the character of the active substance (much as Kendall did in the case of thyroxin). He believed it to be a hydrate of the substance, and he named it "epinephrine." This term has been retained by many writers to describe the true pressor principle.

Priority for the isolation of the pure substance is given to Jokichi Takamine, of Detroit (*Jour. Physiol.*, 1901, xxvii, p. 29; *Proc. Physiol. Soc.*, xxix), although T. B. Aldrich, of Detroit, published his equally effective method for its preparation almost simultaneously (*Am. Jour. Physiol.*, 1901, v, p. 457). By Takamine's method the adrenals are extracted with acidulated water; proteins and other inert substances are removed by heat coagulation and treated with alcohol, and the final solution in a concentrated form is treated with ammonia to precipitate the active substance, which Takamine termed "adrenaline." Repeated precipitations may be used to remove impurities. It may be purified further by treating an acid solution of the partially purified substance with alcohol and ether. After removal of the impurities by filtration, a white crystalline substance is obtained which is fairly pure.

Takamine assigned an empirical formula to his substance, but a slightly different one suggested by Aldrich has been proved correct. Aldrich believed the formula to be $C_9 H_{13} NO_3$. Soon the product was synthesized by the German chemist, A. Stolz (*Ber. d. deutsch. chem. Gesellsch.*, 1904, p. 37),

who showed it to be o-Dioxy-phenyl-ethanol-methylamin of the formula $(OH)_2\ C_6H_3$-CHOH-CH_2-NH(CH_3). This preparation was not so active as the natural epinephrine, although they appeared to be identical chemically. The reason for this was explained later by F. Flächer (*Ztschr. f. physiol. Chem.,* 1908, lviii, p. 189), who demonstrated differences between them and showed that the synthetic epinephrine was a racemic mixture of the *d*- and *l*-epinephrine.† The natural product is the lævo-rotatory form and is as much as fifteen times as active as *d*-epinephrine.

Epinephrine is a weak base, and is most commonly available in medicine in a 1:1000 solution of the hydrochloride. Even in minute quantities, it is a powerful pressor substance. The pressor action is due to constriction of the peripheral blood-vessels, mainly the arteries, and results from its action on the vasomotor system. Constriction of the arterial wall as the result of epinephrine administration is dependent upon the ratio of calcium to potassium in the blood and also upon the pH (M. A. Goldzieher, "The Adrenals," New York, The Macmillan Company, 1929, p. 47). Calcium and acids intensify the effect, while potassium inhibits vasoconstriction. Epinephrine also has a decided effect on carbohydrate metabolism. D. Noël Paton, of Glasgow (*Jour. Physiol.,* 1903, xxviii, p. 286), showed that injections of it cause hyperglycemia and glycosuria in the normal animal. In this, as well as in some other respects, epinephrine is antagonistic to insulin.

STANDARDIZATION—In most methods, the chemical assay of epinephrine depends upon the color reactions given. Probably the most used chemical method of assay is that of Otto Folin and his associates, of Harvard (*Jour. Biol. Chem.,* 1912-1913, xiii, p. 477). They use their special uric acid reagent and their phosphotungstic acid reagent on epinephrine solutions or acid extracts of adrenal tissue. Epinephrine gives three times as much color as uric acid. The blue color developed is compared with that formed by a uric acid standard. Then, too, A. Seidell and F. Fenger (*U. S. Hyg. Lab. Bull.,* 1914, p. 100) use manganese dioxide to oxidize the epinephrine to a pink color, which is compared with a standard colored solution of cobalt chloride and gold chloride in hydrochloric acid.

†"Adrenalin" was the actual term used by Flächer. However, he did not really use or perfect "adrenalin," for this is the trade name given by Parke, Davis & Co. to their original product. The body does not contain adrenalin; the physiological principle is called "adrenin" (W. B. Cannon). Epinephrine, as has been noted, was the name given by Abel to a precursor of the ultimate product of Takamine and Aldrich. The word "epinephrine" was adopted by the American Medical Association to indicate the adrenal medullary principle, and is the name now quite generally used. However, it is manifestly unfair to abstract a paper on some clinical use of "adrenalin," and refer to it as "epinephrine."

Biological methods of assay have been developed making use of almost every physiological reaction of epinephrine and almost every species of laboratory animal from frogs, on whose eyes the mydriatic action of epinephrine is tested, to dogs and cats, used to determine blood-pressure increases. Methods based on the pressor action of epinephrine are most commonly used. The method adopted in the U.S.P. X. is essentially that of E. M. Houghton, of Detroit (*Proc. Am. Pharm. Assn.*, 1901, xlix, p. 351): A standard 1:100,000 solution of epinephrine hydrochloride is made. An anesthetized dog is given sufficient atropine to paralyze the vagi, then a cannula is inserted into the carotid artery and connected with a mercury manometer and kymograph. The standard solution is injected into the femoral vein until the amount necessary to cause a rise in blood-pressure of from 30 to 60 mm. is determined. Then the unknown is injected until it gives the same effect as the standard. By comparison, it is possible to determine the strength of the unknown.

Adrenalin has been called "the first hormone," but this is not true, for medical history shows that secretin holds this distinction. However, it is quite true that adrenalin was the first hormone remedy as well as the original endocrine active principle. A long list of its therapeutic potentialities might be recorded here, but space forbids. Many references to the usefulness of this product are found in other chapters.

THE CORTICAL HORMONE—Since the discovery of epinephrine and its origin in the adrenal medulla, physiologists have directed most of their attention to the medulla and its secretion. The fact that animals deprived of all adrenal tissue die within a short time was believed at first to be due to loss of the medulla, but a large mass of evidence has accumulated to prove that it is the cortex and not the medulla that is essential to life.

Animals deprived of their adrenals may recover at first and for a short time appear to be normal in every respect; but, a few days before death ensues, anorexia and muscular weakness develop and increase until complete collapse occurs. Many vital chemical changes accompany adrenalectomy, of which the following are the most important: The arterial pressure falls (*Am. Jour. Physiol.*, June, 1928, lxxxv, p. 364). The blood becomes very concentrated, with a decrease in plasma (*ibid.*, June, 1926, lxxvii, p. 114). The ability to do work is reduced markedly, 90 per cent. or more in rats (*ibid.*, Sept., 1927, lxxxii, p. 1). The metabolism is reduced to a low level (*ibid.*, Sept., 1928, lxxxvi, p. 360). The animals develop a marked loss in resistance to infections and poisons, such as histamine and typhoid vaccine (*Jour. Exper. Med.*, April, 1928, xlvii, p. 503). Blood chemistry is profoundly influenced. There is a moderate fall in blood sugar and chlorides. There

is a marked rise in non-protein nitrogen, especially urea, and in the calcium (*Am. Jour. Physiol.*, Nov., 1926, lxxviii, p. 711). Phosphorus is increased, and there is evidence of an uncompensated acidosis in the decreased pH, carbon-dioxide tension, serum bicarbonate, and total acid (*ibid.*, Feb., 1927, lxxix, p. 679).

At autopsy a large percentage of completely adrenalectomized animals show much congestion in the liver, kidneys, and especially in the pancreas. Gastric ulceration is not uncommon, and congestion of the mucosa of the whole gastro-intestinal tract is usual (*ibid.*, Nov., 1926, lxxviii, p. 683).

The literature contains reports of various types of adrenal extracts that influence one or more of the symptoms of adrenal insufficiency and that are evaluated from this standpoint. Attempts to produce an extract effectual in preventing fatigue have been successful. At the meeting of the Freiburger Medical Society on March 2, 1926, G. Kühl (*Klin. Wchnschr.*, Aug., 1926, v, p. 1491) stated that adrenalectomized guinea-pigs showed a marked increase in muscle fatigability from 4 to 8 hours after operation. He prepared a series of epinephrine-free adrenal extracts which he injected into these animals, and contractions were renewed for from one to two hours. Other organ extracts had no such effect.

J. Stefl, of the University of Masaryk (*Compt. rend. Soc. de biol.*, Sept. 18, 1928, xcix, p. 985), studied the effect of a hydrogen peroxide extract of adrenals on the fatigued gastrocnemius muscle of the decerebrate frog. The contractions were renewed, resembling those of a fresh muscle. This extract was thermostable. B. Vásárhelyi's extracts (*Magyar orvosi arch.*, 1926, xxvii, p. 251), made from beef adrenal cortex with alcohol and water, increased the work of the rabbit's heart from 10 to 20 times as much as the traces of epinephrine present would account for. It relieved the cramps in pigeons that had beriberi. Another extract called "Cortisupren" has been tested by E. Schmitz and W. Milbradt, on pigeons with beriberi, a disease characterized by a rise in cholesterol and fatty acids. Cortisupren checks this increase (*Ztschr. f. d. ges. exp. Med.*, 1929, lxviii, p. 393).

A substance that stimulates respiration after breathing has ceased in decerebrate cats deprived of adrenal influence was extracted from adrenals by Swale Vincent and J. H. Thompson, of London (*Jour. Physiol.*, Aug., 1928, lxv, p. 449). They called this substance "pneumin."

At the Thirteenth International Physiological Congress, A. Szent-Györgyi, of the University of Cambridge (*Am. Jour. Physiol.*, Oct., 1929, xc, p. 536), reported on the isolation of crystals of a powerful reducing substance from the adrenals. He has identified it as an isomer of glycuronic acid.

It is a powerful catalyst of certain biological oxidations and, in minute quantities, inhibits pigment formation.

Another type of extract has been prepared by A. T. Cameron and F. D. White, at the University of Winnipeg (*Tr. Roy. Soc. Canada,* 1928, xxii, p. 145). By extraction of adrenal cortex with N/10 hydrochloric acid and subsequent treatment with methyl alcohol, a substance was obtained that was capable of accelerating growth in young white rats when administered orally. Still another is the substance known as "cardaissin," which was obtained by Cameron. It is claimed that cardaissin has an accelerating effect on the heart rate in proportion to the amount injected.

In a paper read before the Thirteenth International Physiological Congress, B. Sokoloff, then of Prague (*Am. Jour. Physiol.,* Oct., 1929, xc, p. 521), reported that, in six hundred animals with malignant neoplasms, a single injection of a dialyzed extract of adrenals and iron and sulphuric naphthypararosanilin into the tumor itself caused beneficial changes. Increased oxidation resulted in destruction of these experimental malignant growths. Again, F. Arloing and associates, of Lyons, France (*Compt. rend. Soc. de biol.,* Aug. 13, 1929, ci, p. 1140), prepared glycerin extracts from the adrenals of rabbits having epithelioma. Injection into white mice having epithelioma resulted in the arrest of the growth. (The extract of Coffey and Humber, prepared from sheep's adrenals, has been used with variable results in the treatment of cancer in man. See Chapter 44.)

Since it had become a generally accepted fact that removal of the adrenal cortex resulted in death (in most mammals), physiologists from many laboratories attempted to prepare extracts that would prolong life in adrenalectomized animals. In 1926 F. G. Banting and S. Gairns, of the University of Toronto (*Am. Jour. Physiol.,* June, 1926, lxxvii, p. 100), reported that various types of beef cortical extract did not prolong life or modify the terminal symptoms in adrenalectomized dogs. In fact, in many cases the survival period seemed to be shortened. On the other hand, aqueous cortical extracts prepared from dog adrenals appeared to prolong their lives and gave marked clinical improvement.

At the meeting of the New York Pathological Society, on March 10, 1927, M. Goldzieher, of Brooklyn, reported experiments with an adrenal extract. In June, 1928, he made the statement (*Klin. Wchnschr.,* June 10, 1928, vii, p. 1124) that for two years he had been working on the cortical hormone, to which he had given the name "interrenin." It was extracted with N/5 HCl, precipitated with sodium chloride, and purified by repeatedly dissolving it in 70 and 80 per cent. alcohol. The substance obtained was a

white amorphous powder that was soluble in alcohol and dilute acid. Physiologically, interrenin acted as an antagonist to epinephrine and, when injected simultaneously with it, was capable of neutralizing the action of epinephrine on blood-pressure. Goldzieher tested the potency of his extract on adrenalectomized rats and found that it prolonged life. His work has not found ready acceptance because of this unfortunate choice of an experiment animal, since most operators find that about 50 per cent. of operated rats survive indefinitely (J. M. Rogoff, *Endokrinologie,* Oct., 1929, v, p. 256; H. L. Jaffe, *Am. Jour. Physiol.,* Oct., 1926, lxxviii, p. 453; J. T. Lewis, *ibid.,* May, 1923, lxiv, p. 503). On the other hand, H. M. Evans, of the University of California, has made the observation that all completely adrenalectomized rats die. (See S. W. Britton's excellent review in *Physiol. Rev.,* Oct., 1930, x, p. 617.)

In 1927 F. A. Hartman and his associates in the University of Buffalo (*Proc. Soc. Exper. Biol. and Med.,* Jan., 1927, xxiv, p. 69) contributed their first report on the adrenal cortex hormone, a preliminary report having appeared in the same periodical the year before (March, 1926, xxiii, p. 467). Beef adrenal cortex was extracted with water that was slightly acidified to facilitate filtration, for these solutions contain much protein. The active substance was precipitated from solution by saturation with sodium chloride. An aqueous solution of the substance to which they gave the name "cortin" prolonged the survival period in nineteen adrenalectomized cats. The period of survival ranged from 7 to 60 days as compared with 5 or 6 days for controls. The cats from which the adrenals had been removed through the lumbar path in two stages were given subcutaneous injections of various extracts, the most efficacious product being the salt precipitate extract. This was washed until nearly free of epinephrine. One such extract prolonged the average survival period in ten cats 27.4 days. Another averaged 31.1 days in a series of four cats. (*Am. Jour. Physiol.,* Sept., 1928, lxxxvi, p. 353.)

True to form in endocrine research circles, Hartman has been quite severely criticized for several reasons, chiefly because he used too few controls in his early work, a possible error that he has since corrected. The definite increase in survival periods can hardly be accounted for by variations in surgical technic alone. Then, too, Hartman's early salt precipitate extract was able to prolong life, but he admits that it was not sufficiently potent to prevent indefinitely symptoms of acute insufficiency (*Am. Jour. Physiol.,* Sept., 1928, lxxxvi, p. 360). However, Hartman developed a more concentrated extract (*ibid.,* Dec., 1930, xcv, p. 670) by extracting the cortex with ethyl ether, which dissolves very little of the epinephrine. The ether was

removed by distillation, and the residue extracted with warm 80 per cent. alcohol. Much inert material was then removed by chilling and filtering the extract. After removing the alcohol, the residue was taken up in water. This aqueous solution contained cortin in a concentrated form. By extracting with ether again, the extract was rendered practically free of epinephrine, containing less than 1 part in 100,000, and could be given intravenously.

According to Hartman and his coworkers, this extract maintains normal health in adrenalectomized cats indefinitely, and is capable of reviving animals in the last stages of insufficiency. It maintains normal growth in young adrenalectomized rats, and was used in a comatose patient with Addison's disease (*Clin. Med. and Surg.,* May, 1931, xxxviii, p. 332). The equivalent of 2500 Gm. of fresh cortex was given the first 2 days and 500 Gm. daily thereafter. Within 24 hours the patient was conscious and eating, but died later of pneumonia. The autopsy findings were of interest because the adrenal cortex, although nearly absent, showed areas of beginning regeneration. From this, one is forced to conclude that the extract must have been exerting a homostimulative influence on the remnant of the cortical tissue.

Cortin has a marked influence on the blood-pressure. In a case of Addison's disease, injections of cortin raised the systolic blood-pressure from 50 mm. to 74 mm. in 24 hours, and to 94 mm. in 4 days. At the same time the pulse was reduced from 120 or more a minute to 70.

(It should be added that many clinical tests with other cortical extracts, especially Adreno-Cortin* (*q.v.*) show that the product is not pressor, and can be given in cases with normal or high blood-pressure with no increases. On the other hand, the marked effect on muscle tonicity also improves the cardiovascular tone, thereby raising the extremely low tensions in addisonian and pre-addisonian cases.)

A. E. Koehler, now of Santa Barbara, has also conducted many experiments in this field. He used an acid adrenal extract (*Jour. Am. Med. Assn.,* Nov. 10, 1928, xci, p. 1457) from which he salted out an active substance that was capable of maintaining life in adrenalectomized dogs, and of eliminating such symptoms as asthenia and fatigue in hypoadrenal patients.

Cortin is only one of several cortical extracts developed in the last few years that are capable of relieving symptoms of acute adrenal insufficiency. In fact, for six or seven years J. M. Rogoff and G. N. Stewart, of the H. K. Cushing Laboratory of Experimental Medicine at Western Reserve University in Cleveland, have been working on such an extract. In 1927 they reported the results of their use of extracts of dogs' adrenals prepared with 0.9 per cent. salt solution and glycerin (*Science,* Oct. 7, 1927, lxvi, p. 327).

This was administered intravenously to adrenalectomized dogs. The periods of survival were very slightly lengthened. Then they showed that injection of amounts of epinephrine equivalent to the amount present in the extracts was without effect in prolonging life. Later they prepared an extract of sheep's adrenals (*Am. Jour. Physiol.*, April, 1928, lxxxiv, p. 660). No details of the method used have been published yet; so, when it is stated that from 0.5 cc. to 1 cc. was administered, it is quite impossible to draw conclusions as to the amount of cortex administered. It was given by intravenous injection to twenty-nine adrenalectomized dogs, one of which survived for 78 days. However, from Dec. 23, 1926, to Feb. 13, 1927, when it died, it received only one injection of 1.25 cc. (on Jan. 3). Apparently, some factor other than the extract must have been operating in this animal, but the authors emphatically state that, although most careful search was made for accessory adrenals, none were found. At any rate, since hypercalcemia is noted as one of the terminal symptoms by Rogoff and Stewart and Hartman (perhaps accounted for by blood concentration), it is of interest that at autopsy the parathyroids of this dog—the regulators of calcium metabolism—were found to be of great size.

In the remaining twenty-eight animals, the periods of survival ranged from 5 to 27 days, an average of 11.9 days. Thirty-six controls lived an average of 9.6 days, ranging from 4 days 2.5 hours to 15.75 days. Of the twenty-eight treated animals, five survived longer than any of the controls. In a later paper Stewart and Rogoff (*Am. Jour. Physiol.*, Dec., 1929, xci, p. 254) present the results of treating thirty-two adrenalectomized dogs with an average survival period of 12.5 days. These results appear slightly positive, but hardly striking. The authors have named the active principle in their extract "interrenalin."

Interrenalin was given orally in enteric-coated capsules to seven patients with Addison's disease. Even in severe cases, some alleviation of symptoms was obtained. During the early treatment of the disease, the patients gained in weight, the blood-pressure rose, and fatigue was allayed. Benefit was observed within from two to four weeks after commencing treatment.

Another extract, nameless, but perhaps the most potent one of all, has been prepared by W. W. Swingle, of Princeton University, who also has devoted much time and study to the adrenals. At first, Swingle and J. J. Pfiffner (*Anat. Rec.*, Dec., 1929, xliv, p. 225; also *Am. Jour. Physiol.*, Jan., 1931, xcvi, p. 153) used corn-oil or olive-oil as a solvent for their lipid extract, which they administered subcutaneously. When given to twenty-three bilaterally adrenalectomized cats, the average survival period was 27.8 days as compared with 7.7 days for thirty-eight controls, but it contained epinephrine

and caused serious abscesses. Soon a method was developed for bringing their active substance into solution in water (*Science*, March, 1931, lxxi, p. 321; *Am. Jour. Physiol.*, Jan., 1931, xcvi, pp. 164, 180). The method of preparation is given in greatest detail. Briefly, the cortex from beef adrenals was extracted with 95 per cent. alcohol, which was removed by vacuum distillation, and the residue taken up in benzene. After removal of the benzene in vacuo the residue was extracted with acetone, which in turn was removed by vacuum distillation. At this stage the residue was purified by repeated extractions with 70 per cent. alcohol. The alcohol extract was washed with petroleum ether to remove cholesterol and other inert substances. After removal of the alcohol in partial vacuum, an aqueous extract was made so that 1 cc. represented 30 Gm. of fresh cortex. At this stage the extract contained about 0.38 mg. of epinephrine per cubic centimeter but by filtering the alcoholic extract through permutit practically all the epinephrine was removed, and the final aqueous extract contained one part in two million, a quantity that can be measured by sensitive chemical tests only. This solution is protein-free, pale yellow in color, and relatively large doses may be administered subcutaneously, intraperitoneally, or intravenously without toxic effects. It is capable of reviving and restoring to normal cats prostrate from acute adrenal insufficiency. In daily doses of about 0.5 cc. per kilo, it is capable of maintaining adrenalectomized cats in health indefinitely.

Some of this extract was administered by L. G. Rowntree and collaborators (*Jour. Am. Med. Assn.*, Jan. 24, 1931, xcvi, p. 231) to a number of patients with Addison's disease, in the Mayo Clinic. Even those in a state of collapse were "at least temporarily restored to apparent health" with a total dosage of from 40 to 60 cc. of the extract, which is equivalent to from 1200 to 1800 Gm. of fresh cortex. The appetite improved, the patients gained in weight, the mental depression left, exercise could be taken without undue fatigue, and the pigmentation was lessened. In fact, the symptoms were relieved quite completely and very remarkably. The clinical features of this fascinating subject are considered under Adrenal Disease (35).

Since 1929 a physiologically active cortical hormone has been generally available under the name Adreno-Cortin.* It is made from beef adrenals by a modification of Hartman's method, which is based on the fundamental principles of fractionization in use for years. The final product is a clear solution, free from epinephrine (by the pressor test). It is sufficiently potent to maintain the life and tonicity of bilaterally adrenalectomized cats for months. This extract has been used extensively in many functional and organic adrenal disorders.

[Perhaps it should be stated here that adrenalectomy causes cats to become very limp and inanimate. The action of the cortical hormone on muscular chemistry and tonicity is missed as much in these cases as it is clinically in the ultimate stages of Addison's disease. The alimentary atonicity is an outstanding feature: chewing, swallowing, peristalsis, and defecation are gradually rendered impossible. Coincidentally there is ulceration—gastric, duodenal, and colonic—in the majority of the control animals but never in the cats receiving Adreno-Cortin. This does not necessarily imply that such a measure is of potential value in the treatment of gastric and duodenal ulceration. As yet this has neither been proved nor disproved. However, this product so modifies the muscular features of the treated cats that they not only are kept alive but are actually lively and active as long as the missing hormone is replaced. When it is discontinued even for forty-eight hours the cats become limp, and, while they can be revivified by renewing the administration of the drug, they soon come perilously near the border-line between life and death.

These cats are not only muscularly depleted, but evidently lose certain other faculties. An interesting experience with one of our cats may explain this: As the cat had fleas, it was treated with flea powder. In licking itself, it got some of the flea powder into its system and nearly died, although normal cats do not act in this way. It was noteworthy that, as a result of this poisoning, the cat promptly reverted to its former state of hypoadrenal depletion and could be brought out of it only by considerable increases in the normal daily maintenance dose of Adreno-Cortin. This added to our confidence in the potency of the product.]

Laboratory experiences with this product definitely establish the reality and the characteristics of the hormone, but do not give a method whereby its potency can be measured mathematically. The present figure concerns the amount of fresh tissue used in the production of a given amount of the finished known-to-be potent product, and 1 cc. of Adreno-Cortin represents the cortical hormone in 5 Gm. of fresh cortex tissue.

The therapeutic potency of Adreno-Cortin has been demonstrated in a wide range of musculotonic difficulties. It is of symptomatic value in Addison's disease, especially if the adrenals are not completely destroyed. In the latter case, huge doses must be given and continued. An incident with which I had to do personally may be of interest: A patient in the last stages of Addison's disease, and virtually moribund, received Adreno-Cortin for several days with improvement in his general condition and even in the color of his skin which, of course, was very dark. The alimentary effects were pe-

culiarly good, the extract obviously influencing the emptying of the stomach and the intestinal activity. As treatment proceeded, it was decided to give as much as 20 cc. by intramuscular injection. Following this large dose, the man got up, walked around the apartment, went to the lavatory, sat on the sofa awhile, and finally went back to bed. Soon the effects of the hormone wore off, and the patient was as limp and moribund as before. Some time later he died.

Adreno-Cortin is not sufficiently potent to be used as a dependable measure in ultimate Addison's disease. By far the largest amount of this substance that has been used since 1929 has been in chronic myasthenia and toxic difficulties—especially the cachexia of cancer, the depletion of chronic alimentary disorders with stasis, and post-infectious depletions with hypoadrenia.

Early in our experience with Adreno-Cortin it was suggested that this obvious effect on the muscular chemistry might be of prospective value in hyperthyroidism (63). It has been used in many cases as a means of controlling the cardiac symptoms. The same thing has happened in pneumonia, and it is believed that the effect is that of a catalyst to the muscular chemistry. In these instances, the heart muscle is not only poisoned by the disease itself but is swathed in the wastes of its own overactivity. I frankly believe that Adreno-Cortin intervenes in the chemical matters that go on in the muscle of the heart and intestines and in other muscular structures.

As the reader will see elsewhere (81), this same muscular influence has been employed in Parkinson's disease and other myotonic conditions with definite symptomatic benefit in a generous proportion of cases, but with no fundamental curative effects.

Adreno-Cortin is given by intramuscular injection. The dosage varies with conditions, ranging from 1 to 5 cc. daily or every other day. The corresponding product for oral administration is not quite so free from epinephrine and contains 0.35 per cent. of the medullary principle—not enough, however, to interfere with the predominant cortical action that is desired. The effect of this substance on the alimentary musculature, as well as on all other muscles, is especially helpful in chronic diseases because it facilitates the disposal of excessive fatigue poisons, not only of the muscles of the bowel itself, but of the liver and other organs in which there is a muscular element. The tone is raised; there is prompt subjective as well as objective improvement; in fact, when Adreno-Cortin is given by mouth, some patients note a marked alimentary tonic effect within the first week; others, if the dosage is pushed beyond a certain indeterminate point, will complain of cramps and fleeting alimentary discomfort due to the hypertonia.

STANDARDIZATION—The standardization of the cortical hormone has been attended with considerable difficulty because the only absolute method for the determination of the activity of the extract is on adrenalectomized cats and dogs; and the time and extract required, as well as the surgical technic involved, preclude this method from use in routine biological assay. Various methods have been suggested tentatively, including that of F. A. Hartman (*Proc. Soc. Exper. Biol. and Med.,* Jan., 1930, xxviii, p. 94), who says: "The minimum amount of cortin necessary to maintain the growth of young adrenalectomized rats serves as a basis for assaying the potency of extracts." This would be evidence of the activity of an extract, but not suitable for assay until further refinements have been made.

Other methods have been based on the fact that the resistance of adrenalectomized rats to poisons and infections is markedly reduced. They succumb to small doses of typhoid vaccine (J. Marmorston-Gottesman and J. Gottesman, *Jour. Exper. Med.,* April, 1928, xlvii, p. 503). D. Perla and J. M. Gottesman (*Proc. Soc. Exper. Biol. and Med.,* Feb., 1931, xxviii, p. 475) have tested the effects of cortin in the neutralization of the effects of typhoid vaccine in adrenalectomized rats. Adrenalectomized three-months-old rats, after receiving two injections of Hartman's concentrated extract daily, were able to stand 4 M.L.D. of typhoid vaccine on the sixth day following operation, and 3 M.L.D. of histamine. One M.P.D., or 1 minimal protecting dose is the smallest amount that will protect against 1 M.L.D.

Others have attempted to standardize this hormone by testing the effect of extracts on fatigued muscle. This has not been developed successfully. Provided the action of the extract is sufficiently specific, it would seem that the method has possibilities.

At present it is only possible to identify and verify the potency of the cortical hormone by its capacity to maintain life in adrenalectomized animals, preferably cats, and to measure this tolerably well by noting the amount needed per kilo of the animal's weight.

ADRENAL PRODUCTS

Medulla

ADRENALIN (1A)—The adrenal medullary hormone made available in crystalline form in 1901. Usually obtainable in solution, 1:1000, though the crystals themselves are available. Its highly vasoconstrictive action makes adrenalin a powerful astringent and hemostatic as well as a heart stimulant. It is obtainable in many forms—ointment, suppositories, inhalant, etc.—with and without suitable synergistic remedies. Adrenalin is standardized by its pressor influence. *(Parke, Davis & Co.)*

ADRENALIN "CIBA" Synthetic (1A)—The synthetic product is claimed to be identical in every respect with the natural product. It is pure and stable. *(Society for Chemical Industry in Basel.)*

ADRENIN (3)—A physiological term suggested by Sir E. S. Schafer, used freely by Walter B. Cannon, and accepted by the *Journal of Physiology*. It refers to the adrenal medullary hormone in vivo.

CARDAISSIN (2)—A substance obtained by Cameron from bovine adrenal glands by neutral alcoholic extraction and purified by fractional precipitation. It increases the heart rate but has no adrenalin effects such as vasoconstriction. It has no effect on the voluntary muscles.

EPINEPHRINE (1A)—Epinephrine was the name given to a product prepared by J. J. Abel, of Johns Hopkins Hospital, which was supposed to be the adrenal medullary principle. It was found, however, not to be the finished product. Later this name was selected for the adrenal medullary hormone to avoid using the trade name "adrenalin." Epinephrine is now made and sold under this name by many firms, and is chemically identical with adrenalin.

HEMISINE (1A)—A name given to an epinephrine product previously called "Adrenalin B. P." *(Burroughs Wellcome & Co.)*

SUPRARENALIN (1A)—The adrenal medullary hormone obtainable in vials of 1 gr. or in stable, water-white solution, 1:1000. *(Armour and Company.)*

SUPRARENIN (1A)—The name given by von Fürth in 1903 to an adrenal medullary principle. It is an almost white, finely granular, odorless, crystalline substance, nearly insoluble in water, alcohol, or ether. Available in solution, as the chloride (in physiological saline solution 1:1000). *(I. G. Farbenindustrie A.-G., Berlin.)*

Cortex

ADRENO-CORTIN* (1A)—A solution of an adrenal cortex fraction free from epinephrine (by the blood-pressure test), each cubic centimeter containing the equivalent of 5 Gm. of fresh cortex. The product is not really standardized physiologically; rather its potency is verified by its capacity to maintain life and tonicity in bilaterally adrenalectomized cats, and to restore tonicity after its discontinuance has caused the animals to become limp. (This product was the first one of its kind available to the profession, but it is not potent enough to substitute for the adrenal hormone in advanced Addison's disease.) Indicated in hypoadrenia in all degrees, and as a muscular detoxicant and sthenic agent in alimentary stasis, etc., Parkinson's disease, heart conditions in hyperthyroidism, pneumonia, etc. Dose: In cancer, 1 cc. daily; in asthenia, 1 or 2 cc. daily or every other day; in addisonism, from 5 to 20 cc. daily, intramuscularly.

ADRENO-CORTIN CAPSULES* (1B)—A desiccated extract of adrenal cortex tissue mechanically freed from medulla and containing 0.35 per cent. epinephrine. Each 5-gr. capsule represents 2 Gm. (30 gr.) of fresh gland. Dose: From 1 to 3 capsules a day.

CORTIN (2)—The adrenal cortical hormone perfected by F. A. Hartman and associates, of Buffalo. In concentrated solution free from epinephrine, each daily dose in Addison's disease representing the cortex hormone in 150 beef adrenals (approximately 500 Gm.).

CORTISUPREN (1B)—A German trade preparation of the total substance of the adrenal cortex (virtually free from epinephrine). In tablets and solution. *(Laboschin, Berlin.)*

INTERRENALIN (2)—The name given by G. N. Stewart and J. M. Rogoff, of Cleveland, to a concentrate containing the adrenal cortex hormone in glycerinated solution for oral administration, the potency of which is determined by administration to adrenalectomized dogs.

INTERRENIN (2)—An experimental adrenal cortical product separated by Max Goldzieher, of Brooklyn.

SUPRARENAL CORTEX (1B)—Desiccated adrenal cortex in powder and tablets (1 gr.). Assay of this product for epinephrine finds it completely absent—evidently accomplished by washing. Dose: From 1 to 5 tablets three or more times a day. *(Armour and Company.)*

10. THE DUODENUM

Secretin—Purifying Crude Secretin—Cholecystokinin—Present Methods of Extraction—Duodenal Products.

PECULIARLY ENOUGH, "the original hormone" was separated from scrapings of the duodenal mucosa, and its discoverers, W. M. Bayliss and E. H. Starling, of London (*Proc. Roy. Soc., London,* 1901-1902, lxix, p. 352; *Jour. Physiol.,* 1902, xxviii, p. 325), called it "the pancreatic hormone" because of its remarkable effects on the pancreatic secretion. Later it was named "secretin." As has been related (page 42), the term "hormone" was coined to apply to substances of the same general nature as secretin.

SECRETIN—These workers in the Institute of Physiology in University College were trying to explain some of the conclusions of I. P. Pavlov and his associates (I. L. Dolinsky, *Arch. d. sc. biol.,* St. Petersburg, 1894, iii, p. 399) regarding the digestive cycle, and particularly the properties of the tryptic activator, enterokinase, which not so long before had been discovered by N. P. Chepovalnikov, one of Pavlov's assistants. In 1901, L. Popielski, another of Pavlov's associates, called attention to the fact that the introduction of a dilute solution of hydrochloric acid into the duodenum causes a marked flow of pancreatic juice. This effect was believed by the St. Petersburg workers to be purely nervous.

But Bayliss and Starling found that the injection of acid or acid chyme into a loop of duodenum was followed by a secretion of pancreatic juice, even when all nerve channels had been severed. These investigators were convinced that the message from the intestine to the pancreas was carried through humoral channels.

After Bayliss and Starling had demonstrated that an injection of acid into a denervated loop of duodenum was followed by a secretion of pancreatic juice, they scraped off the mucosa from fresh duodenum and jejunum, macerated it with hydrochloric acid, filtered and neutralized the solution, and, eureka! it caused a copious flow of active pancreatic juice in the experiment dogs. They called this active pancreatic stimulant "secretin." But, as they were unable to extract it from other tissues or without acid, they were led to believe that secretin did not exist as such in the tissues but was in the form of an inactive substance, prosecretin, which was hydrolyzed by acids into the active form, secretin.

To this day the existence or non-existence of prosecretin has not been settled. Since secretin has been extracted by various inert solvents, such as saline solution, it is evident that it exists to some extent in the free form

in the mucosa; but the fact that the activity of extracts is so markedly increased by acids supports the theory that it exists in some other form.

The Russian workers, however, called Bayliss and Starling's idea "the secretin theory," even though they had shown that the effect on the pancreas was chemical and that it occurred even when all the nerves to the pancreas were severed.

As has been the case in a dozen similar experiences, there was some bandying of words, but the air was cleared by A. Hustin, of Brussels, who in a one-hundred-page thesis published in 1913 removed the last prop from under the structure built by the St. Petersburg school.

Hustin dissected the pancreas from a dog while an assistant made a secretin-bearing extract of its duodenum. The pancreas, placed in liquid paraffin overlaying water kept at 38° C., was irrigated with liquids, which were introduced by means of a cannula through the pancreaticoduodenal artery and were conveyed away by another cannula in the portal vein. A third cannula was introduced into the duct of Wirsung, to lead off the pancreatic juice. As a result of numerous experiments, Hustin established the important fact that a pancreas irrigated independently with Locke's physiological serum, blood, or secretin solution gives no secretion, but irrigation with a mixture of blood and secretin gives an abundant secretion of clear liquid containing trypsinogen, lipase, and amylase—results that can hardly be gainsaid. The author further states that, in the impregnation of the pancreatic cell, secretin is used up in a manner that renders it sensible to the action of certain substances in the blood. For convenience Hustin compares this action with the side-chain theory of Ehrlich, *viz.*, that living protoplasm carries certain chemoreceptors or contains chemoreceptive substances, and it is by combination with these that drugs, etc., induce their specific effects.

Still further confirmation of Bayliss and Starling's deduction that they were dealing with a hormone from the pancreas has come recently from Ivy and his associates at the Northwestern University (*Am. Jour. Physiol.*, Sept., 1927, lxxxii, p. 27), who showed that acid stimulation of an intestinal transplant causes secretion in a pancreatic transplant.

PURIFYING CRUDE SECRETIN—Any consideration of the development of secretin must necessarily include a discussion of the substances that were originally extracted with secretin and whose properties were assumed to be those of secretin itself. At least two of these substances have been separated in a form sufficiently pure for effective study.

Bayliss and Starling noted that their extract was contaminated with vasodilatins and a substance that caused increased bile flow. Many methods

were evolved for the preparation of a vasodilatin-free secretin, but the method of M. M. Weaver and his associates in the University of Chicago is one of the simplest and best (*Jour. Am. Med. Assn.*, Aug. 28, 1926, lxxxvii, p. 640), and has been used as a basis for further purifications by others. By this method from 100 to 150 cm. of fresh intestine is washed free of débris, and 100 cc. of 0.4 per cent. hydrochloric acid is introduced into the intestinal section, which is closed with hemostats. After half an hour this extract is filtered and nearly saturated with sodium chloride. The sodium chloride precipitate (secretin) is thoroughly washed to remove traces of vasodilatins, and when dissolved in water is a powerful pancreatic secretory stimulant, free from vasodilatins.

From the standpoint of therapeutic possibilities, the impurity in crude secretin which causes hypoglycemia is exceedingly interesting. J. Freud and Saadi-Nazim, of Paris (*Compt. rend. Soc. de biol.*, July 23, 1926, xcv, p. 571), working with dogs, introduced hydrochloric acid into the duodenum and noted that the secretin formed induced the secretion of pancreatic juice and at the same time caused a decrease in blood sugar. E. Gley and R. Hazard, of Paris (*ibid.*, June 8, 1928, xcix, p. 16), carried this a step further and interpreted their findings as indicating that the secretin stimulates the pancreas to secrete the internal secretion, insulin. Experiments of E. Zunz and J. LaBarre, of Brussels (*Bull. Acad. roy. de méd. de Belgique*, 1928, viii, p. 801), demonstrate that crude secretin increases insulin secretion. Their results have been confirmed by J. LaBarre and E. U. Still, of the University of Chicago (*Am. Jour. Physiol.*, Jan., 1930, xci, p. 649).

Evidence of the stimulating influence of crude secretin on the islets of Langerhans is presented by H. H. Dale, who has shown that repeated injections are followed by an increase in the size and number of the islets. However, L. Takács, of Hungary (*Ztschr. f. d. ges. exp. Med.*, 1927, lvii, p. 527; also 1928, lx, p. 424), has shown that crude secretin has a hypoglycemic action on totally diabetic dogs.

Thus proof has been given that the hypoglycemic factor in crude secretin acts in two ways: (1) It augments the secretion of insulin by stimulating the islet tissue. (2) It has an action of its own, similar to the action of insulin, which results in hypoglycemia. It is not insulin, since incubation with pepsin-HCl does not destroy its activity.

This hypoglycemic substance has been separated from secretin by LaBarre and Still (*Am. Jour. Physiol.*, Jan., 1930, xci, p. 649), with acidified 90 per cent. alcohol. The secretin passes into solution completely. Its action is the same as that of crude secretin. Still (*ibid.*, Jan., 1930, xci, p. 405) has

prepared the hypoglycemic substance, which, in doses of 10 mg. intravenously, lowers a dog's blood sugar from 330 mg. per cent. to 200 mg. per cent. in two hours, and a normal dog's blood sugar from 110 mg. per cent. to 63 mg. per cent. Neither peptic nor tryptic activity destroys it.

CHOLECYSTOKININ—Cholagogue action is consistently present in crude secretin preparations and even in all the purified extracts reported, with the exception of that of Takács. Evidently the substance causing bile formation is an additional impurity that has not been eliminated so successfully as the others.

The gall-bladder evacuant that contaminates crude secretin has been removed not only from secretin extracts, but has been prepared in very active form by A. C. Ivy, of Northwestern University, Chicago. He calls this substance "cholecystokinin" (*Am. Jour. Physiol.*, May, 1928, lxxxv, p. 381). A concentrate is prepared from secretin solutions obtained by the salt precipitation method of Weaver, Luckhardt, and Koch, by precipitation with trichloracetic acid. Its solubility in alcohol differs from that of secretin, pancreatic secretin being soluble in absolute alcohol while cholecystokinin is only very slightly soluble in concentrations of over 80 per cent. Thus cholecystokinin can be prepared without secretin and vice versa.

Cholecystokinin prepared by Ivy's method yields a product containing from three to four parts of secretin to one of cholecystokinin, which, when administered intravenously in doses ranging from 3 to 6 mg., causes gall-bladder contraction.

At the present time it is believed that secretin per se has only one faculty, namely, its stimulating effect on the external secretion of the pancreas. All the other properties originally ascribed to it belong to the substances contaminating the extracts. A great volume of work has been done in an effort to develop a method for obtaining a uniform yield of a pure secretin.

PRESENT METHODS OF EXTRACTION—In 1928 J. Mellanby, of St. Thomas's Hospital, London (*Jour. Physiol.*, Sept., 1928, lxvi, p. 1), reported on the isolation of secretin, but his method has not been used with very much success by other investigators. One of the purest preparations reported is that of Still (*Am. Jour. Physiol.*, Jan., 1930, xci, p. 405), who starts his extraction according to a modification of the method of Weaver, Luckhardt, and Koch, which includes initial extraction with dilute acid and precipitation of crude secretin with salt. The crude secretin in solution, free of vasodilatins, is again precipitated by trichloracetic acid, according to Ivy, and the precipitate extracted with acid 90 per cent. alcohol. This extracts the secretin with a little impurity and leaves most of the cholecystokinin and all the hypogly-

cemic substances in the residue. More impurities are removed by precipitating them with brucine and pyridine. Then the secretin is precipitated with acetone and ether. After an additional extraction with methyl alcohol and precipitation by ether, a fine, white, amorphous product is obtained which is active in promoting pancreatic secretion in doses of from 0.02 to 0.1 mg. per kilo in 10-kg. dogs. It has no other physiological action. It contains 6.66 per cent. nitrogen and no phosphorus, and the reactions for protein are either weak or negative. However, it has not been isolated in crystalline form.

Ivy and his associates (*Am. Jour. Physiol.*, Oct., 1930, xcv, p. 35) have since prepared a product of about equal potency from hogs' intestines. The crude, dry powder is stable for at least a year. The purified product is not destroyed by boiling in water for one hour, but it is destroyed by boiling in acids or alkalies.

Two methods of assay for secretin have been published. The first was suggested by Ivy, who defines a threshold dose of secretin as that amount "which, when injected intravenously, will cause a ten-drop increase in the rate of flow of pancreatic juice within a ten-minute period following the time of injection as compared with the preceding ten-minute period." According to Ivy's method, the first two yards of a hog's gut yields from 75 to 100 doses of secretin.

E. U. Still (*Physiol. Rev.*, July, 1931, xi, p. 328) uses a potent preparation of his own as a standard in his assay. He injects 4 mg. of the standard and measures the pancreatic flow. Then, after this stimulation has worn off, he injects 4 mg. of his unknown, and measures the rate of secretion. He completes his test by again injecting the standard. Apparently an unknown of potency equal to his standard contains one unit.

DUODENAL PRODUCTS

CHOLECYSTOKININ (2)—An experimental fraction separated by A. C. Ivy, of Chicago, from duodenal extract which exerts a marked contractile effect upon the walls of the gall-bladder.

DUODENAL EXTRACT (1B)—Duodenal powder, one part equal to eight parts of fresh scrapings. Dose: From 5 to 10 gr. at meals.

DUODENIN (1B)—A desiccation of duodenal mucosal scrapings from the hog, containing secretin and enterokinase in tablets (1 gr.). *(Armour and Company.)*

PAN-SECRETIN CO.* (1B)—A tablet containing equal parts of an acid extract of duodenal scrapings with a concentrate from the islet cells in the tail of the pancreas. Used as a homostimulant of pancreatic function, both digestive and endocrine. Dose: From 15 to 30 gr. t.i.d.

SECRETIN (2)—An acid extract of the scrapings from the upper twenty-four inches of the small intestine. Used experimentally by intravenous injection.

SECRETOGEN (1B)—A secretin product put up in tablets containing a homostimulative extract from the duodenum, and as an elixir containing extracts from both the stomach and duodenum; also containing 0.1 per cent. HCl. Dose: From 1 to 3 tablets (or teaspoonfuls) after meals. *(G. W. Carnrick Co.)*

11. THE GONADS

I. THE OVARIES: *The Ovarian Cycle—Endovarin,* Ovarin, Oophorin—Ovarian Residue — The Female Sex Hormone, Folliculin, Menformon, Theelin—The Estrins—Standardization.* II. THE CORPORA LUTEA: *The Luteal Cycle—Progestin, Lutin—Corpus Luteum — Flavéine — Lutein — Agomensin and Sistomensin—Lipo-Lutin—Endoluteum.** III. THE TESTES: *Spermin and Spermin Extract—Séquarine and Testikulin—Androkinin—Experimental Therapy — The Male Sex Hormone — Standardization — Lydin*—Endocrine Products from the Gonads.*

THE GONADS, or essential sex glands, are among the most vital of the endocrine organs. While they are not essential to life itself in the sense that the adrenals are, they are vital to the perpetuation of life.

As with many endocrine organs, the gonads render two services to the organism: (1) They produce the essential reproductive cells, the ova and the spermatozoa; and (2) they produce several chemical substances which serve to correlate the functions that contribute to the utility of the reproductive cells. The secondary sex characteristics depend for their initiation and development upon these and other internal secretions, and in no phase of experimental endocrinology can their spectacular effects be more decisively demonstrated than in the prestidigitations possible in this field.

Besides these two cooperative services, endocrine and exocrine, it is believed that the gonads produce important principles that have much to do with the nutrition and health and, apparently, with the circumstances related to the changes in the bones due to age. There is also some evidence connecting the waning gonad function in both sexes with the susceptibility to cancer (44).

The search initiated centuries ago by Ponce de Leon has stirred many a worker. While hope after hope has been dashed to the ground, and sneer after sneer has been cast at those who have tried but failed, the reader is assured that the accomplishments in this long search are indeed very real and as wonderful as any in the whole field of endocrine research.

I. THE OVARIES

The actual endocrine functions of the ovaries depend upon hormones originating in no less than four places: (1) the ovarian tissue or stroma, (2) the corpus luteum, (3) the graafian follicle (follicular fluid), and (4) the corpus luteum of pregnancy. Apparently these four substances are different from one another in functional activity also.

The stromal hormone and the follicular hormone (also known as the female sex hormone, or estrin) will be considered here, but the luteal

hormones will be discussed separately, for they appear to be the physiological antitheses of the ovarian hormones.

THE OVARIAN CYCLE—The current conception of the cause of menstruation is that the follicular hormone (in the graafian follicular fluid) stimulates the development in the follicle of an ovum, which when ripe bursts its follicular covering and releases the ovum into the abdominal cavity in the vicinity of the fallopian tube. This sequence of events is activated by an estrin (estrus-producing hormone) from the anterior lobe of the pituitary gland, with the cooperation of the thyroid, and under the influence of a principle originating in the ovarian stroma.

The corpus luteum produces an internal secretion which is an antestrin or antiovarian hormone, one function of which is to prepare the uterine wall for the nesting of the ovum—a so-called "nidatory hormone." If, however, this specially prepared endometrium is not needed, *i.e.,* if the ovum is not fertilized, the entire layer is discharged. This miniature labor is the menstruation. After the accompanying hemorrhage is over, further uterine flow is checked by a combination of physiologically opposite hormone influences, part of which originate in the corpus luteum.

We see, therefore, that three active principles play the main parts in this vital sequence: (1) the follicular hormone, or female sex hormone, or estrin; (2) the ovarian hormone, a stromal product which is largely a nutritional factor and perhaps a means of contact through humoral channels, with the other closely associated endocrines; and (3) the luteal hormone (or chalone, for it is in reality a true antihormone), or antestrin. The activity of all three of these hormones is now believed to be initiated by the anterior pituitary (18).

It can easily be surmised that variations in the relative proportions of these endocrine principles may be responsible for variations in the functions they control. An excess of the follicular hormone can cause precipitate ovulation, while irregularities in the development of the corpus luteum can cause modifications in the amount and character of the luteal principle with corresponding interference with menstruation.

ENDOVARIN,* OVARIN, OOPHORIN—These and several other names have been given to the ovarian or stromal hormone or to products containing it. This principle is a fundamental factor in regulating the female sex cycle with influences on the accessory reproductive organs—the uterus, the vagina, and the mammæ.

It was believed originally that the ovarian hormone in some manner directly regulated ovarian function and the production of this same hormone.

Especially was it thought that the maturation of the graafian follicle was the real cause of estrus. But F. H. A. Marshall and W. A. Wood, of Cambridge (*Jour. Physiol.*, Oct., 1923, lviii, p. 74), showed that rupture or ablation of the maturing follicles failed to prevent estrus. W. Blair Bell, of Liverpool ("The Sex Complex," London, Baillière, Tindall and Cox, 1916, p. 47), also reports having grafted rabbit ovaries from which the follicles had been removed, with the resultant production of normal estrus.

OVARIAN RESIDUE—A preparation of ovarian tissue, freed as far as possible from the corpora lutea of pregnancy, *i.e.*, the residue after the luteal tissue is cut away, came into prominence in 1919 when W. P. Graves, of Harvard University (*Surg., Gynec., and Obst.*, Dec., 1919, xxix, p. 537), reported a long series of clinical experiences with it. To all intents and purposes, this is total ovarian substance or a stromal extract. It is used in hypovarism and especially during the climacteric as a means of lessening the suddenness of the ovarian loss expected at this period, and consequently as a means of sparing the associated glands from undue need for concern (80).

More recently Max Cutler, of New York, finds this variety of ovarian extract of particular value in the control of mastodynia (70), and outlines some clinical experiences that are self-explanatory.

THE FEMALE SEX HORMONE, FOLLICULIN, MENFORMON, THEELIN—The essential feminine hormone is of preeminent importance in the physiology of woman, since it presides over the development and functioning of the reproductive mechanism. In view of its influence on the sex cycle and the fact that its influence was first scientifically demonstrated in relation to estrus or rut in small animals, this substance has been called an estrin.

Among the early investigators of the ovarian hormone and its physiological action, L. Frankel, of Breslau, Germany, and E. Herrmann (*Monatschr. f. Geburtsh. u. Gynäk., Jan.*, 1915, xli, p. 1) deserve particular mention. Working independently they separated from the ovaries and the placenta an active substance of similar character to the graafian hormone developed in detail by E. Allen and E. A. Doisy at St. Louis University in 1923 (*Jour. Am. Med. Assn.*, Sept. 8, 1923, lxxxi, p. 819). Parallel with the work of Allen and Doisy, E. Laqueur, of the University of Amsterdam (*Proc. Roy. Acad. Sc.*, Amsterdam, 1925, xxviii, No. 10) perfected a similar product now called "Menformon." In fact, I believe that the Dutch product was the first of its kind to be made available to the profession.

Folliculin was made available by me in 1926. At first it was actually made from follicular fluid, and the product contained only 5 rat units per cubic centimeter. Later, when E. C. Dodds, of London, showed that this active

principle was obtainable in far greater concentration from the placenta, work with Folliculin was replaced by Plestrin,* which contains five times the unitage of the former product (19).

There is much more that might be related here. Robert T. Frank, of New York, quite recently published a 320-page book on this subject entitled "The Female Sex Hormone" (Springfield, Illinois, C. C. Thomas, 1929). However, record must be made of the crystallization of the estrin, or female sex hormone, from the urine of pregnant women. This technical triumph was accomplished by E. A. Doisy and his associates at St. Louis University, and a potent crystalline extract is now available under the name "Theelin." The most recent announcement of these workers concerns the differentiation of still another estrogenic principle from the urine of pregnant women. This has been called "theelol," and it is six times as active as Theelin according to tests in immature female rats (*Jour. Biol. Chem.*, May, 1931, xci, p. 641). In spayed animals, however, Theelin is twice as active as the new product.

THE ESTRINS—The hormone principles capable of producing estrus have been called estrins. Their consideration is just a little complex in view of the fact that similar substances, which exert definite effects on the ovarian cycle, are found in the anterior lobe of the pituitary, the placenta, and amniotic fluid, as well as in the urine and blood of pregnant animals. There are chemical differences between these substances, but they are alike in the one respect that they arouse estrus and menstruation—rut in mice and rats, and menstruation in monkeys. From a clinical point of view, these principles found in Folliculin, Œstrin, Plestrin, Apestrin, or Ovestrin, are somewhat similar. Some of the more readily obtainable ones are used in an effective way, which is discussed elsewhere (80).

Since supplies of these various estrins are no longer obtainable from the follicular fluid or the ovaries, it seems best to refer to them under other headings; hence Apestrin is considered with the pituitary principles (18) and Plestrin with the placenta (19). There necessarily is a little duplication, for which apology is made.

STANDARDIZATION—The various methods of separation need not be outlined here, but the means whereby the female sex hormone is identified and standardized is of special interest. It happens that in rodents estrus occurs every four or five days and is accompanied by characteristic changes in the vaginal secretion. The review by Henry S. Finkel, of Boston (*New England Jour. Med.*, May 21, 1931, cciv, p. 1094), outlines this clearly:

"The cycle may be described in four stages. During the first stage, called *di-estrus,* the ovaries contain immature graafian follicles, the uterus is in the resting state, the vaginal smear consists of polymorphonuclear leukocytes. During the second stage, called *pro-estrus,* the ovaries contain ripening follicles, the uterine endometrium is undergoing proliferation, the vaginal smear is made up of nucleated epithelial cells. During the third stage, called *estrus,* in which copulation takes place, the ovaries contain mature follicles on the point of rupturing, or already ruptured; the uterus is distended with secretion; the vaginal smear is composed of squamous epithelial [or cornified] cells. During the fourth stage, called *met-estrus,* the ovaries contain corpora lutea at the site of the ruptured follicles, the uterus is undergoing retrogression, the vaginal smear consists of degenerated squamous cells and fresh leukocytes. If the ovaries are removed, the estrous cycles are abolished, as a result of the withdrawal of the ovarian influence, and the uterus and vagina remain in the resting state. If graafian follicle fluid is then injected into these ovariectomized mice, an artificial cycle is induced, which manifests itself by the successive changes in the uterus and vagina characteristic of pro-estrus, estrus, and met-estrus, with a return to the di-estrous condition after the effect of the injection has worn off.

"These facts form the basis of the biological test for folliculin called, after the originators, the Allen-Doisy test. The substance to be tested is injected into ovariectomized mice or rats. If folliculin is present, the cells in the vaginal smear change in approximately forty-eight hours from leukocytes to squamous cells, with a return of leukocytes after the folliculin has been eliminated. The test can also be used quantitatively in terms of mouse or rat units, one unit being the amount of hormone which is just sufficient to give a positive reaction in an adult castrated mouse or rat, respectively. One rat unit is approximately the equivalent of five mouse units."

Folliculin was found also to have a remarkably potent trophic influence, and was used first in the treatment of conditions of utero-ovarian infantilism and especially in sterility. As far back as 1926 this product was used with decisive success in endocrine sterility, despite the fact that it was of far less potency than present preparations.

This trophic test turned out to be of great assistance in my work. Supplies of Folliculin, and later of Plestrin, were sent to several workers including E. C. Dodds. The report came back that it was virtually inert as an estrus-producing substance. Our tests were repeated, confirming the previous findings. As a result, two important points were developed: (1) Variations in the procedure used to perform the test give varied results; hence there is a need for the standardization of standardization measures. (2) Qualitatively, the trophic test is by all odds the most spectacular and dependable means of demonstrating the activity of this substance. This test consists in administering the product intramuscularly to an immature female rabbit

for several days. When the series of injections is completed, the rabbit and a control from the same litter are killed, and the uterus, horns, ovaries, and tubes dissected out from each and weighed. The expected trophic increase resulting from the standard product is 1000 per cent., but occasionally increases as great as 1500 per cent. are seen. Such evidence is quite incontrovertible.

Because of the early work (1926-1927) on the trophic effect of this principle, the majority of those using Plestrin have been led to employ it in hypoplasia and sterility rather than in hypovarism and menopausal disorders. As a matter of fact, the climacteric is essentially a period when utero-ovarian atrophy is normal and, too, the endocrine problems at this period are not merely ovarian but involve the related glands and call for other forms of organotherapy (80).

II. THE CORPORA LUTEA

The corpus luteum (more properly given the plural name, corpora lutea) is a part of the ovaries and is an essentially endocrine tissue. Each ovary contains a certain number of immature follicles, one of which matures periodically in connection with ovulation. The incretory character and purpose of the corpus luteum formed after ovulation have been quite thoroughly developed and confirmed, chiefly in the laboratory, but in an increasing way in the clinic also.

It should be stated at the outset that there are two types of corpora lutea: (1) those "spurious" structures that come to naught from month to month as a result of the failure of impregnation of the ovum, and (2) the larger and more stable "corpus luteum of pregnancy," which differs decidedly in appearance and characteristics from the ordinary variety. This is a vital and permanent structure which, for certain definite physiological reasons, follows its cycle of growth and recession.

THE LUTEAL CYCLE—The changes resulting from the influence of the corpus luteum have been quite strikingly shown in experimental work with various small animals. For example, in the rabbit, estrus proceeds spontaneously only up to the point of maturation of the follicles. Ovulation does not occur except after the stimulus of coitus, at which time the follicles rupture and the corpora lutea are formed. During this period of ripening, the endometrial cells proliferate under the influence of the follicular hormone (estrin) already referred to. A few days after the formation of the corpora lutea, the endometrium undergoes a much greater hypertrophy, the so-called "progestational proliferation" which prepares the uterus for the nesting of the ovum. This proliferation takes place whether fertilization has occurred

or not, and the reaction in the non-fertile cycle is called "pseudopregnancy" because of its resemblance to the changes of early pregnancy. Now, if a rabbit's ovaries are removed shortly after impregnation, these progestational uterine changes do not occur, and the embryos degenerate and are aborted.

PROGESTIN, LUTIN—The specificity of the luteal action has been demonstrated conclusively by W. M. Allen and G. W. Corner, of the University of Rochester (*Am. Jour. Physiol.,* March 1, 1929, lxxxviii, p. 326), who caused progestational proliferation in ovariectomized animals by the administration of a corpus luteum extract. These workers recommend the name "progestin" for this hormone, because of its protective function in connection with gestation. However, additional evidence is now available to prove that the corpus luteum hormone is really a dual principle or two hormones: one "progestin," causing the effect just referred to; and the other with an estrus-inhibiting effect, to which the name "lutin" has been given. This "second luteal hormone" has quite a wide-spread influence, essentially antiovarian in character. During the active life of the corpus luteum, the maturation of the graafian follicles is inhibited and the uterine contractility lessened. (The uterotonic stimulus caused by pituitrin is lessened or entirely lost during the luteal phase. This hormone, lutin, also exerts a nidatory effect as well as a stimulating influence on the mammary tissue.

Continuing from the review by Finkel (*loc. cit.,* p. 1906):

"The function of lutin, therefore, is the preparation of the uterus for the nidation of the ovum, the preparation of the breasts for lactation, and the protection of the developing embryo. Lutin is incapable of producing its specific effects unless the tissues have been previously prepared by the presence of folliculin. If the injection of lutin into an ovariectomized rabbit is delayed until the animal's folliculin has been eliminated, the progestational proliferation of the endometrium does not take place. Folliculin and lutin, therefore, are complementary; folliculin is responsible for the changes in the organism up to the time of copulation and fertilization; lutin brings about the further changes necessary for the continuation of pregnancy."

With these physiological variations in mind, and with much other information made available from many hundreds of animal experiments, there is laid before us the prospect of being able to bring about in a clinical way changes somewhat similar in character, if less in degree, to those that are brought about in the laboratory.

CORPUS LUTEUM—Preparations containing the corpus luteum hormone are used therapeutically (1) to inhibit ovarian activity and menstruation during pregnancy, (2) to facilitate the nesting of the impregnated ovum, and (3) to balance ovarian irregularities that are dependent upon the im-

balance between these hormone influences due to nutritional changes, hypoplasia, etc., in the ovarian structures, and to changes in the amount and character of the hormone stimuli from without, such as the effects known to come from the anterior lobe of the pituitary and the thyroid.

These three physiological influences make corpus luteum therapy of value (1) in ovarian irritability and menorrhagia, (2) in controlling attempts at menstruation during pregnancy and therefore preventing abortion, (3) in overcoming certain phases of the early toxemia of pregnancy, and (4) in quite a wide range of endocrine upsets due to disturbance of the luteal-stromal equilibrium.

FLAVEINE—Much of the early research work in this field has been done in France. In fact, it was J. A. Lebreton, of Paris, who first used an extract of corpus luteum in contradistinction to the entire ovarian extract. This was reported in the thesis, "Opothérapie ovarienne: Rôle du corps jaune," published in 1899, and it is interesting to note that the clinical indications were the vomiting and other toxic symptoms of early pregnancy. There are numerous French extracts, among them a product known as "Flavéine," from the Latin *flavus,* yellow. (Free corpora lutea of pregnancy are yellowish in color, and, indeed, their French name is *corps jaune,* "the yellow body.") Flavéine is an extract somewhat similar in nature and therapeutic indications to the American Lutein.

LUTEIN—A desiccated extract from the corpora lutea of the sow was brought before the profession of this country in a practical way as the result of the work of Curtis F. Burnam, of Baltimore, starting about 1904. According to him (*Jour. Am. Med. Assn.,* Aug. 31, 1912, lix, p. 698):

"When given by mouth, corpus luteum of the sow, even in large doses, has little or no toxic effect on women.

"It affords us a valuable means of controlling the nervous symptoms which occur in so many patients at the time of the natural or artificial menopause, giving relief to most sufferers.

"It is a valuable remedy in treating patients with insufficient internal ovarian secretion during the menstrual life. This class constitutes a very large number of women.

"It is an excellent remedy to induce menstruation in young women suffering from functional amenorrhea. Those who are fat, in addition to regaining menstruation, usually, but not always, lose weight.

"There would seem to be a possibility for the drug in cases of unexplained sterility and repeated abortions. . . .

"So far as it goes, my work strengthens my conviction that Fraenkel is correct in attributing menstruation to the internal secretions of the corpus luteum."

Of course, this was written nearly twenty years ago and many new ideas have been perfected since then. None of these, however, nullify the fundamental conclusions of Burnam and many others; and now, as then, Lutein is of definite therapeutic service whether it is given by mouth or by injection, or both.

It seems that the explanation of the clinical ovarian-stimulating influence of Lutein, in face of the fact that the luteal hormone has indeed an ovarian-inhibiting influence, comes about as a result of what has been called "stimulation by offense." It is as though the ovarian influence dares the ovaries or arouses them indirectly.

Because ovarian irregularities so often depend upon shortcomings outside the pelvis, it seems that the rational thing to do in cases manifesting ovarian insufficiencies—both functional and hypoplastic—is to encourage the depleted ovarian regulators. This leads us to the consideration of the pluriglandular therapy of the ovarian trinity (80).

AGOMENSIN AND SISTOMENSIN—Two of the differentiated luteal extracts, known as Agomensin and Sistomensin, were perfected in Switzerland some years ago (L. Seitz, H. Wintz, and L. Fingerhut, *München. med. Wchnschr.*, 1914, lvi, p. 1657). Sistomensin is a luteolipoid extract containing the specifically active hormone of the corpus luteum. For some time it was recommended as "a physiological regulator in menstruation and in cases of hypertension." This substance and its twin, Agomensin, are prepared from the corpus luteum; but, since these two substances (the luteolipoid and the luteamin) exhibit different properties as regards their solubility in different solvents, the Swiss workers found it possible to separate them.

Sistomensin, then, is a luteal product that exerts a prohibitive influence on menstruation. As is the case with other luteal products previously mentioned, it has been recommended chiefly in certain types of menorrhagia and dysmenorrhea. More recently, however, since a number of other standardized preparations of the female sex hormone have been made available, the biological characteristics of Sistomensin appear to have been changed. It is now offered as "an extensively purified ovarian hormone" capable of bringing about both experimental and clinical responses similar to those obtained from the female sex hormone or estrin.

Agomensin, on the other hand, is a luteamin which is used to activate the menstrual cycle in cases with hypofunction. In contradistinction to Sistomensin, it is used in functional amenorrhea, genital hypofunction, and the disturbances incident to the menopause. Both these products are given by mouth or by intramuscular injection.

LIPO-LUTIN—Some of the endocrine principles are fat-soluble, or of lipid nature. The lipid principle from the corpus luteum has been made available under the name of "Lipo-Lutin." This substance is obtainable in suspension for injection and is used to "increase the luteal hormone preponderance" thereby counteracting the tendency to uterine contractions that may occur at menstruation or in early pregnancy. It will be seen that this influence has a place in the control of pain and discomfort due to uterine spasm at menstruation, as well as in the overruling of the tendency towards abortion in early pregnancy.

This principle, like other corpus luteum extracts, is used also in the control of certain types of nausea and vomiting of pregnancy (84) and in functional menorrhagia (80).

ENDOLUTEUM*—There is a very large number of corpus luteum preparations in various forms from which the physician can make his selection. Endoluteum has been available for a number of years for both oral and hypodermic use. Recently, however, it has been found possible to evaluate its potency in an experimental way and thus to standardize it physiologically. This seems to be an advance over previous practices, and not only has made it possible to determine the potency of the extract but, because of this, to improve it.

Endoluteum was the first biologically tested corpus luteum hormone to be made available, and it may be of some interest to the reader to explain how this came about:

Judging from the physiological data already marshalled, the luteal hormone is a physiological antithesis of the follicular hormone. Since this latter is an estrin, the former can properly be called an antestrin—opposed to estrus. Based on this, a method of testing was perfected by H. T. Graber and R. A. Cowles, of Detroit (*Proc. Soc. Exper. Biol. and Med.*, June, 1931, xxviii, p. 977), whereby normal ovarian activity is suppressed and therefore the state of estrus is prevented or postponed. This, of course, is exactly opposite to what is accomplished by means of the estrus-producing hormone. In the biological testing of Endoluteum, certain amounts are injected hypodermically into female rats thereby causing the interval between the estrus cycles to be markedly lengthened—from 200 to 300 per cent. Eventually a mathematical factor undoubtedly will be based on this method, and I predict that the potency of products of this nature will be evaluated in antestrus units just as the female sex hormone and other similar principles are standardized in estrus units (rat units) by the method of Allen and Doisy, already referred to (page 96).

III. THE TESTES

A review of the struggle to isolate and to utilize the male sex hormone takes us back to the founding of modern organotherapy when the value of testicular extracts was demonstrated in a spectacular way. Although testicular organotherapy itself fell into disgrace because of the avidity with which the quacks and charlatans took it up, this foundation-stone which has lain out in the weather for many years, has at last found its place in the building; and, even though it may not prove to be a corner-stone, it is an important part of the structure.

It was on June 1, 1889, that C. E. Brown-Séquard, Professor of Physiology in the University of Paris and editor of *Archives de physiologie,* the most important journal of physiology of its day, made his famous address before the Paris Société de Biologie. Brown-Séquard had made an extract from the testes of dogs, which he administered to himself at the age of seventy-two, establishing to his own satisfaction that this emulsion had therapeutic possibilities of definite worth (*Arch. de physiol. norm. et path.,* 1889, xxi, p. 651). This event is variously appreciated. For example, Victor Robinson, of New York, in his outstanding work, "Pathfinders in Medicine" (New York, Medical Life Press, 1929, p. 586), says:

"In the wilderness of ignorance, Brown-Séquard had opened a path which has since grown into one of the main-traveled roads of modern science. Even so conservative an endocrinologist as R. G. Hoskins regards June 1, 1889, as the 'definite birthday' of the science of the internal secretions, and Arthur Weil states that on that day Brown-Séquard laid the corner-stone of endocrinology."

On the other hand, C. R. Moore, of the University of Chicago (*Jour. Am. Med. Assn.,* Aug. 22, 1931, xcvii, p. 518), very recently referred to this same accomplishment in the introduction to his article, "The Regulation of Production and the Function of the Male Sex Hormone," thus:

"Attempts at the therapeutic administration of the male hormone to man perhaps logically date from the unsubstantiated assertions of Brown-Séquard that a glycerin-water extract of testicles injected subcutaneously is an effective agent in prolonging the productive period of a man's life—physical as well as mental."

During the first four years of the clinical application of this idea (1889-1893), reports were made by more than twelve hundred physicians. Their conclusions were essentially the same as many of those of more recent years, with the possible exception that the channel of action is now known to be different, the influence being brought about through humoral rather than nervous paths.

SPERMIN AND SPERMIN EXTRACT—Not long after Brown-Séquard's reports, Alexander von Poehl, a professor at the University of St. Petersburg (*St. Petersb. med. Wchnschr.*, 1890, xv, p. 271), suggested that certain organs produced remedial agents with which the organism was able to regenerate itself and thus overcome disease. From a number of organs, chiefly the testes, he isolated a crystalline substance that he called *sperminum* and which he believed to be the active principle of Brown-Séquard's extract. This substance, however, had been discovered in Holland by P. Leeuwenhoek, in 1678—more than two hundred years before. It was rediscovered by Vauquelin in 1791, and studied by Schreiner (*Ann. d. Chem. u. Pharm.*, 1878, cxciv, p. 68), also by A. Ladenburg and J. Abel (*Ber. d. deutsch. Chem.*, 1888, xxi, p. 758); but von Poehl's investigations disclosed its catalytic oxidative action and introduced it to clinical use. Spermin is distributed widely in nature, and, although it is a principle of undoubted activity, it is not capable of physiological standardization.

"Spermin extract" was the name given by me in 1918 to an extract of the interstitial cells of Leydig, rich in the essential endocrine material, the potency of which was demonstrated experimentally as well as in practice. It should not be confused with the crystalline product perfected by von Poehl. There is a great difference between replacing a missing organ or its influence and encouraging a functionally depleted one.

But, important as all this work with spermin has been, the efforts of von Poehl and others have proved to be a digression, for spermin was not the true hormone. So, let us return to our starting-point with Brown-Séquard.

SEQUARINE AND TESTIKULIN—The testicular preparations made by Brown-Séquard in 1889 were crude water or glycerin extracts from the testes of dogs and guinea-pigs. Among numerous names given to this extract were Séquarine, in France, and Testikulin, in Germany. Although this product was improved upon by A. d'Arsonval (*Arch. de physiol. norm. et path.*, 1894, xxvi, p. 172), who stabilized it by using glycerin as a preservative and by autoclaving or filtering it through porcelain, nevertheless the extract contained numerous tissue constituents in much lower concentration than in the fresh tissue.

In 1896, Oskar Zoth (*Arch. f. d. ges. Physiol.*, 1896, lxii, p. 335), also Fritz Pregl (*ibid.*, p. 379), using glycerin preparations supplied by a commercial laboratory, proved that this testicular principle increases muscular energy and delays the onset of muscular fatigue. This was determined by means of Mosso's ergograph, records being made on these workers themselves as well as on others.

Some time later P. Ancel and A. Bouin, of Strasbourg (*Compt. rend. Acad. d. sc.,* 1906, cxlii, p. 232), using subcutaneous injections of an extract similar to that of Brown-Séquard, prevented atrophy of the penis and seminal vesicles in castrated guinea-pigs. In the same year C. E. Walker, of Liverpool (*Proc. Roy. Soc. Med.,* 1906, i, p. 153), caused comb and wattle growth in hens by injecting saline extracts from cockerels' testes. As will be seen shortly, this was a forerunner of the current laboratory procedure of physiological standardization.

ANDROKININ—As a result of the work of S. Loewe, begun more than ten years ago in the University of Dorpat, Esthonia, an active product called Androkinin has been developed. Apparently this is a testicular concentrate containing other things than the active principle. Loewe and his associates believe that the active principle in Androkinin is the male sex hormone. They find it in normal ox blood, and outline a technical method for separating it (*Klin. Wchnschr.,* July 26, 1930, ix, p. 1407). Besides developing a potent therapeutic agent, these workers seem to have hit upon a clinical test of potency, which, however, is far too technical to be used in practice. Several German reports confirm the therapeutic potency of this substance as a sthenic and restorative agent, but there is good ground to question whether all the improvement credited to the remedy really comes directly from it alone.

EXPERIMENTAL THERAPY—This tonic effect is the basis for testicular organotherapy. Many clinical reports confirm such therapeutic claims, but the critics say that other circumstances, including psychic influences, might have been responsible for the benefit. While there is no denying this, it is hard to see how psychic effects can cause the responses in experimental work. For example, R. G. Hoskins, of the Harvard Laboratory for Neuro-Endocrine Research (*Endocrinology,* July-Aug., 1925, ix, p. 277), has shown that testicular feeding, with comparatively crude products given by mouth, brings about a remarkable increase in the vigor and energy of rats. Hoskins' method of determining this was a semimathematical one, involving the use of the whirling rat cage, the revolutions of which were numbered and recorded.

Since then, L. L. Stanley, of San Rafael, California, whose recent work has arrested the attention of the physiologists as that of no other, has reported a laboratory test of the tonic effect of quite crude extracts which is noteworthy, even if it is a "fish story." It was observed by Stanley that when gold-fish were fed finely ground whole testes (rams') they were considerably more

active than when fed other ordinary foods. An apparatus was devised whereby the movements of the fish were recorded graphically.

A diagram of the equipment and tracings made during these experiments will be found in an article by L. L. Stanley and G. L. Tescher (*Endocrinology,* Jan.-Feb., 1931, xv, p. 55). The graphs are astonishing, and, as these authors say:

"It is seen that with shrimp food the fish in twenty-four hours made 1648 movements. With the testicular food during an equal period they made 6828 movements, an increase of 400 per cent. These tests were repeated three different times with approximately the same results."

THE MALE SEX HORMONE—Because of the early difficulties in obtaining a standardizable hormone from the testes, various workers have turned their attention to other sources. F. Caridroit and A. Pézard, of the Collège de France in Paris (*Compt. rend. Soc. de biol.,* July 2, 1926, xcv, p. 296), demonstrated the presence of the male hormone in the blood of cocks. H. Busquet, also of Paris (*ibid.,* Dec. 2, 1927, xcvii, p. 1463), found it in the blood of various young animals, particularly bulls, and reported encouraging results from its oral administration.

S. Loewe and H. E. Voss, of Mannheim (*Klin. Wchnschr.,* July 15, 1928, vii, p. 1376), using the seminal vesicles of the castrated mouse, demonstrated the presence of the male sex hormone in the urine of men, but chose not to disclose the details of their work.

The most notable work done with urine, however, is that of Casimir Funk, Benjamin Harrow, and A. Lejwa, of New York (*Proc. Soc. Exper. Biol. and Med.,* Jan., 1929, xxvi, p. 325; *ibid.,* April, p. 569; *Am. Jour. Physiol.,* March, 1930, xcii, p. 440), who have found a method of preparing a definitely active extract from human urine of sufficient potency to replace the function of the testicles in capons. Their extract was an evaporated filtrate obtained from an alcoholic precipitation of a concentrate of urine. These workers observed that the male hormone content in the urine is greatest just after puberty and that the amount diminishes as age advances. But so far no preparation of this nature has been made clinically available, as has its female counterpart.

STANDARDIZATION—A. Pézard (*Compt. rend. Acad. d. sc.,* 1911, cliii, p. 1027) was the first to use the capon as a subject on which to test the hormone affecting male secondary sex characters. He showed that ovarian grafts cause the comb and wattles to diminish in size and become pale, and the feathers to take on female characteristics, but that testicular grafts

emphasize masculinity. He found that the equivalent of "one-tenth of a cryptorchid hog testis," injected twice weekly into Orpington capons, caused a growth of comb, wattles, and ear-lobes, as well as producing more masculine behavior. His method is not described. In 1926, B. S. Ssentjurin, of Leningrad (*Ztschr. f. d. ges. exp. Med.,* 1926, xlviii, p. 712), reported having experimentally inhibited regression of the size of the comb in capons by injecting Locke's solution perfusates from bulls' testes.

It is along similar lines that physiological standardization of the male sex hormone finally has been accomplished. The task begun by Brown-Séquard was finished in the University of Chicago by a group of workers in the Department of Physiological Chemistry, under the direction of F. C. Koch, and in the Department of Zoology, under the supervision of C. R. Moore. This was the immediate result of the work reported by L. C. McGee (Ph. D. Dissertation, University of Chicago; *Proc. Inst. Med. Chicago,* 1927, vi, p. 242), in which was given the first clear-cut evidence of extracting, fractionating, and evaluating the hormone from testicular tissue.

This Chicago group (T. F. Gallagher and F. C. Koch, *Jour. Biol. Chem.,* Nov., 1929, lxxxiv, p. 495; *Jour. Pharmacol. and Exper. Therap.,* Nov., 1930, xl, p. 327) have devised a "bird-unit" scale, the unit of which is the daily amount required to produce an average increase of 5 mm. in the combs of five brown Leghorn capons in five days. In addition to this, C. R. Moore and T. F. Gallagher (*Jour. Pharmacol. and Exper. Therap.,* Nov., 1930, xl, p. 341) define a rat unit in terms of dosage that effects complete replacement of the endocrine secretion of the testes; this is about six times greater than the bird unit. Regarding the work of McGee and others, F. C. Koch (*loc. cit.*) says:

McGee "repeatedly obtained a lipin fraction from bulls' testes which, when injected into brown Leghorn capons, produced marked growth of comb, wattles, and ear-lobes; and, when injected into the castrated guinea-pig, prevented the usual atrophy of the seminal vesicles. Subsequently he, and Gallagher in collaboration with C. R. Moore and his students, showed that the same extracts previously standardized on the capon also correct the cytologic and other accessory gonad changes observed in the castrated rat and guinea-pig."

Early in 1927, Loewe and Voss (*loc. cit.*), who were working independently of those in the Chicago laboratory, reported using the regeneration of the seminal vesicle of the castrated mouse as a test. Their conclusions were similar to those of McGee and Gallagher.

The method of extraction devised by McGee, Gallagher, and Koch is given briefly by Koch (*loc. cit.*) as follows:

"The testes, after being freed from epididymes and tunics, are finely hashed and extracted for three or four days at room temperature with from 3 to 4 volumes of 95 per cent. alcohol. The alcoholic solution obtained is concentrated under diminished pressure until an aqueous emulsion or suspension of lipins is obtained. This is then repeatedly shaken with equal volumes of benzene and the combined benzene extracts again evaporated under diminished pressure. The resulting lipin mixture is next dissolved in acetone and cooled to 10° C. The clear acetone solution is separated from the inert precipitate and again evaporated under diminished pressure. The product thus obtained can be further purified by partition between hexane and various percentages of alcohol in water, resolution in ether, and shaking the ether solution with aqueous sodium bicarbonate, sodium hydroxide, and acids. The final product can be made to be of an activity such that from 0.01 to 0.03 mg. daily causes an appreciable comb growth in a capon in five days. One milligram of such an extract represents from 12 to 18 pounds of testis tissue."

In addition to the avian method of assaying testicular extracts, there are four mammalian tests: the spermatozoon motility test (guinea-pig), the electric ejaculation test (guinea-pig), the prostatic cytology test (several different elements—rat), and the seminal vesicle test (rat). According to Moore and Gallagher (*Am. Jour. Physiol.*, July 1, 1929, lxxxix, p. 388), all these tests have proved that the extracts injected were able to substitute for the internal secretion of the testicle. They have found no castration changes that failed to respond to the injections.

LYDIN*—Since 1918 I have carried on experiments in the attempt to concentrate an active male gonad extract, as well as to perfect the products then available. At first, desiccations of the entire glands from various sources were used; later, based on the work of Alexander Lipschutz, of Dorpat (*Endocrinology*, Jan.-Feb., 1923, vii, p. 1), the more specifically endocrine tissue in the interstitial cells of Leydig was concentrated; and, still later, since the impetus given to fractionization in this field—by the perfection of insulin from the pancreas in 1922 (15) and Anabolin* from the liver in 1925 (13)—the same methods were applied to other glandular material, including both gonad structures. As a result, products of much greater concentration were prepared, and, as the newer knowledge of standardization (*q.v.*) became applicable, it was found possible to increase this potency materially.

The outcome of these twelve years of research is Lydin,* which is believed to contain the essential male sex principle—the counterpart of folliculin. It is far different from previous extracts, for each cubic centimeter of the solution represents the active principle in 220 Gm. of fresh tissue. The desic-

cation figure is 1:108. Lydin was made generally available in 1928, and since then several thousand physicians have used it in a clinical way with what they have reported as good, though not spectacular, results (58).

Now the attitude of the research workers, made obvious from time to time since 1890, has not changed with regard to the clinical possibilities of products of this nature. In consequence, it was clearly necessary for them to neutralize the growing weight of evidence that was accumulating in a dozen different countries, to a small part of which attention has been called. The workers in the University of Chicago are quite sure that Lydin is inert—by their methods and in their chosen dosage. The most recent pronouncement from this source (*Jour. Am. Med. Assn.*, Aug. 22, 1931, xcvii, p. 518) adds to their record of pessimism. C. R. Moore, in discussing this whole subject in an admittedly masterly fashion, not only reiterates his opinion about Lydin, but even denies that homostimulative testicular organotherapy is possible. In fact, he goes much further and questions the whole phase of endocrine therapeutics known as homostimulation. Here is what he says:

"To my knowledge, there is no single criterion or set of criteria that clearly indicates in man a hypogonadal state of the testicle. . . . As to the effect of the hormone on the testicle, it may be said in general that no endocrine gland has been proved to be stimulated by an internal secretion which the organ itself produces. . . .

"Up to the present time I am unaware of any active hormone preparation on the market. One biologic house preparing capsules for oral administration has circularized the medical profession with literature, giving prominence to the names of workers at the University of Chicago (Koch, Gallagher, Moore) with the implications that their preparations have proved active by tests we have developed and employed. One gains the impression that this product has our stamp of approval. We have assayed purchased samples of this product by two different methods (capon comb and spermatozoon motility test) and failed to find any indication of activity in the dosage prescribed."

There are two sides to every question, and I cannot agree with several of these conclusions. The capon test is, of course, no criterion of clinical value, but it does give an idea of the comparative potency of various products. Other feeding tests in fish and mammals and clinical experiences have caused many to come to conclusions at variance with Moore's, but this is not the first time that such differences have arisen in this field, as the careful reader will observe.

The position taken by these workers is unfortunate to say the least, for not only do they deny the potency of Lydin, which is more or less an insignificant matter, and insist that functional testicular disorder, or "a hypo-

gonadal state of the testicle," does not exist, but they attack one of the most vital fundamentals in the whole range of endocrine therapy—the principle of homostimulation.

Despite the fact that this has been discussed elsewhere (page 56), it seems advisable just to mention here that there are antidotes to Moore's pessimism. For example, John T. Halsey, of Tulane University, in the chapter on "Organotherapy and Hormonotherapy" ("Endocrinology and Metabolism," New York, D. Appleton and Company, 1922, Vol. I, p. 89), remarks:

"It is thought by many that in some cases at least of myxedema and cretinism the thyroid feeding brings about favorable changes in the condition of the more or less atrophied thyroid glands. . . . Just as it acts beneficially on the function of various organs, it [thyroid therapy] may also improve the function and perhaps, too, restore to a healthy state such thyroid tissue as may still be present and able to function."

Many physicians have discovered that thyroid therapy does not act only in a substitutive way, and it is well known that the response to thyroid differs materially in different patients. The markedly hypothyroid person requires and can stand large doses of thyroid, whereas the normal individual would be seriously upset by such doses. What is the reason for this? Is it dependent solely upon the amount of material that is given? No, indeed! It is due to the fact that in the myxedematous patient there is little or no thyroid tissue that can respond to the administered thyroid, whereas in the normal or hyperthyroid person the thyroid medication arouses activity on the part of the gland which causes the far greater clinical response. Referring to this same matter, Halsey (*ibid.*, p. 90) states:

"That thyroid administration can exert an influence on the thyroid gland tissues is shown by the results of thyroid therapy in goitre. That it can strikingly stimulate thyroid function seems proved by the disastrous results which have followed thyroid feeding in some cases of exophthalmic goitre."

Still further, in another foot-note, in referring to the "unmistakably favorable effect" of thyroid therapy on certain simple goitres (*ibid.*, p. 93), Halsey says:

"The actuality of this action has been most conclusively demonstrated not only by thousands of clinical observations but also in such experimental studies as those of Bruns who, by examination of segments of the goitre, removed before and after the administration of thyroid, was able to demonstrate histologically that tissue changes of a beneficial type had resulted."

Another hint along these same lines is found in a report from F. A. Hartman, of Buffalo (*Clin. Med. and Surg.*, May, 1931, xxxviii, p. 332),

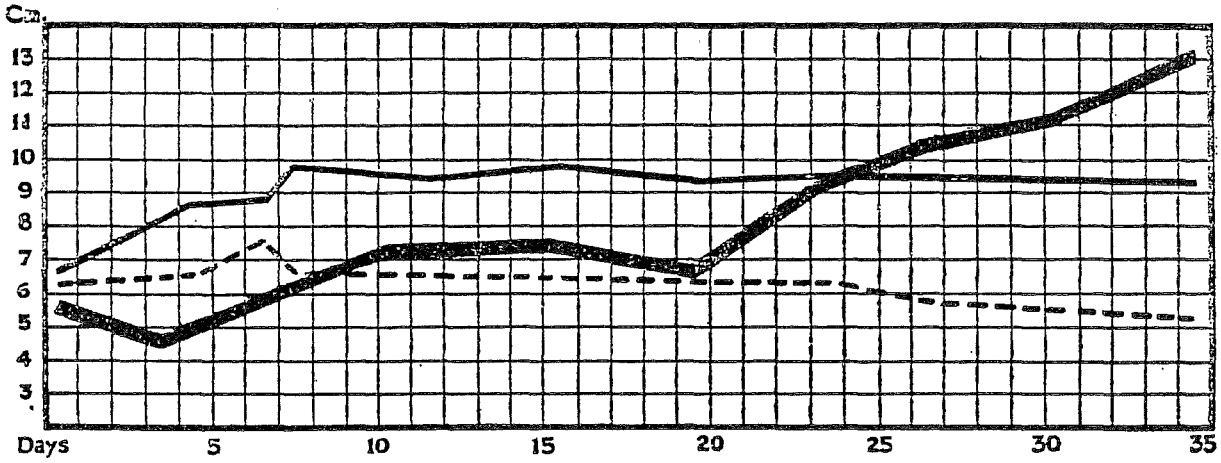
regarding the adrenal cortex hormone. After explaining the character and potency of this principle, an interesting case is recorded regarding which it must suffice to say that

"This patient finally died of pneumonia, and the autopsy showed an almost complete absence of adrenal cortex; but *areas of beginning regeneration were present.*

"There are minor degrees of adrenal insufficiency which are definitely not Addison's disease. In these cases the administration of cortin results in a marked increase in the ability to do work without fatigue and in the sense of well-being. Such a result permits a definite diagnosis of minor adrenal insufficiency."

It might be added that this result not only permits the confirmation of the diagnosis of hypoadrenia, but adds to the conviction that the adrenals have been encouraged to do better work by the homostimulative organotherapy.

Much more that could be added has been told elsewhere, so this defense of homostimulative therapy must be concluded with the remark that many a reader will have had occasion to compare the clinical responses from ovarian therapy in patients with menopausal difficulties that have come about normally with those that have resulted from surgery. The response to ovarian therapy in the latter case is never so good as in the former. The reason is, I am sure, that in the non-surgical case there is still ovarian tissue that can respond to the homostimulative influence of the ovarian product and thus supplement its substitutive therapeutic influence.



But, to return to the consideration of Lydin, it can only be stated that it has been both fed to and injected into capons with measurable changes in comb growth. Just one graph is reproduced, indicating comb-growth variations in three cockerels: a normal control (thin line), a capon (thick line), and a capon control (dotted line). This test has been repeated many times, and the *appearance* of the comb and wattles is changed just as remarkably as

their *size*. The combs of the castrated birds wither and atrophy, taking on a sickly yellowish-red color, while those of the treated birds are healthy and muscular, bright red in color, and are seen to grow with unusual rapidity. Of course, when the treatment of these capons is discontinued, their combs and wattles begin to pale and droop. Later, when the birds are killed, autopsy must confirm a complete elimination of the testes.

Another word about the therapeutic potentialities of Lydin: It has decided limitations, which I have never failed to emphasize. Obviously, structural atrophic conditions such as follow mumps do not respond to it (73). Clearly, the testicular hormone, no matter how potent nor how generously dosed, will not affect hypoadrenia or hypothyroidism! The picture of maximal hypogonadism in its ultimate form (dystrophia adiposogenitalis, eunuchoidism, etc.), is more often due to hypopituitarism (83) than to any other non-anatomical (destructive) cause. Hence, if any form of organotherapy is likely to help such functional phases as may be amenable to any kind of treatment, *it will be pituitary rather than testicular therapy*. This I have stated all along—years before Lydin was perfected.

Finally, since the clinical picture of asthenia, depletion, impotence, etc., which follows influenza or other acute or chronic toxemias, patently must affect the body as a whole rather than only small parts of it, it is decidedly in order to broaden the treatment. This is the best reason for pluriglandular therapy in such circumstances, as well as the best excuse for the pessimism previously referred to and for the limitations of Lydin.

Exactly the same thing has occurred time and again in other phases of endocrine dysfunction and their treatment, and, as the reader will see elsewhere (5), this is the best explanation of the limitations attributed in some quarters to ovarian therapy.

As for the far-reaching influence of the gonads on other endocrine functions, as well as of each glandular entity in its individual rôle in the regulation of gonad function, William T. Belfield, Chicago urologist (*Jour. Am. Med. Assn.*, April 19, 1924, lxxxii, p. 1237), makes the following interesting observations:

"It seems probable that gonad therapy also, begun as an irrational attempt at an impossible 'rejuvenation,' may emerge from the disrepute of its infancy and develop into a valuable means for relieving ailments that are not now associated with gonad deficiency; for it is demonstrated that the gonad does not originate sex; that it is less essential to the maintenance of sex than is the thyroid or the suprarenal; and that it is indeed one of a chain of interacting endocrine glands, efficiency in every link of which is essential to normal function, sexual or somatic."

ENDOCRINE PRODUCTS FROM THE GONADS

Ovary

ENDOVARIN* (1B)—A clear, straw-colored, stable solution of the active water-soluble principles of whole ovary, each cubic centimeter of which represents 23 gr. of fresh ovarian tissue from the cow. Dose: 1 cc. or more daily.

FANDORINE (1B)—A tablet composed of total ovarian and mammary extracts, together with certain antispasmodic principles. Used in vasomotor imbalance of the menopause, metrorrhagia, etc. Dose: From 1 to 3 tablets t.i.d. *(Etablissements Chatelain, Paris.)*

FOLLICULIN* (2)—The follicular hormone isolated by fractionization of the follicular fluid of the graafian follicles of the corpora lutea of hog and beef ovaries. In solution for intramuscular injection. Each cubic centimeter is standardized to contain 5 Doisy rat units. Now replaced by Plestrin* (19).

FOLLICULINE (1A)—The female sex hormone obtained from ovaries and available in ampules of 2 cc. Physiologically standardized to contain 10 "physiologic units" in each ampule. Used in ovarian dysfunction. Dose: 2 cc. daily by intramuscular injection. *(Laboratoires Choay, Paris.)*

MENFORMON (1A)—The follicular hormone or "Ovarialhormon" after E. Laqueur. In isotonic aqueous solution, free from albumin, physiologically standardized, each ampule containing 40 mouse units (equal to about 10 rat units) with trikresol 0.3 per cent. as a preservative. Dose: 1 ampule daily or every two or three days. *(Degewop Gesellschaft A.-G., Berlin.)*

OVARIAN EXTRACT (1B)—A desiccated extract of whole ovaries, one part of which is equivalent to seven parts of fresh tissue. In powder, tablets, or capsules of various sizes. Also in solution, each cubic centimeter containing the water-soluble extract derived from 23 gr. of fresh tissue. Dose: From 5 to 10 gr. t.i.d. and/or 1 cc. intramuscularly daily or every other day.

OVARIAN RESIDUE (1B)—A desiccation of the dried tissue remaining from ovaries after the corpora lutea have been mechanically removed. Preparation is similar to that described for Lutein (below). In tablets of 3 gr. Dose: 1, 2, or 3 tablets, usually t.i.d. *(Hynson, Westcott, and Dunning.)*

VARIUM (1B)—Whole ovarian substance in 5-gr. tabloids. Each tabloid represents the amount of fresh tissue indicated. Dose: 1 or 2 tabloids increased to 4 or 5, twice or three times a day. *(Burroughs Wellcome & Co.)*

Corpus Luteum

AGOMENSIN (1B)—An extract from the corpus luteum containing luteamin, which activates the menstrual cycle and fosters sexual development. Available in tablets of 1/3 gr. and in ampules. Each cubic centimeter of the solution represents two tablets. Used in amenorrhea, hypovarism, and retarded sexual development. Dose: 1 or more tablets t.i.d. and/or 1 cc. daily. *(Society for Chemical Industry in Basel.)*

ENDOLUTEUM* (1B)—A desiccation of the corpus luteum from the ovaries of cows. One part equal to about six parts of the fresh material. In tablets of 2 and 5 gr. Dose: From 1 to 3 tablets t.i.d.

ENDOLUTEUM SOLUTION* (1A)—A stable solution of the luteal principle, physiologically standardized by its antestrous influence on mice and rats. An arithmetical factor, "antestrous unit," is based on the amount of the active principle required to postpone estrus a varying number of days beyond the norm. Each cubic centimeter contains the amount of antestrin in 75 gr. of fresh corpora lutea of pregnancy. Used in vomiting and nausea of pregnancy, the tendency to abortion, and in menorrhagia. Dose: 1 cc. or more daily. Preferably supplemented by the corresponding product by mouth.

LUTEIN (1B)—A desiccation of the corpora lutea of the ovaries of hogs, representing tissue "as nearly as possible as found in the animal gland." The materials are not degreased, treated with solvents, or modified in any way. Tablets of 5 gr. Indicated

in dysovarism and its various manifestations. Dose: From 1 to 3 tablets t.i.d. *(Hynson, Westcott, and Dunning.)*

LUTEIN SOLUTION (1B)—A solution of corpus luteum, each cubic centimeter containing the modified water-soluble extractive of 2 dg. of dried substance. Dose: 1 cc. daily or every other day by deep intramuscular injection. *(Hynson, Westcott, and Dunning.)*

SISTOMENSIN (1A)—A corpus luteum hormone (luteolipoid) that exerts an inhibitory influence on menstruation. It is put up in tablets of 1/5 gr. and in ampules containing the equivalent of four tablets per cubic centimeter. It is given in excessive menstruation—menorrhagia, metrorrhagia, and hemorrhage occurring at the menopause and during puberty. Dose: 1 or more tablets t.i.d. and/or 1 cc. daily. *(Society for Chemical Industry in Basel.)*

Testes

ANDROKININ (2)—A name given by S. Loewe to the male sex hormone, which was found in fresh ox blood, also in urine.

DIDYMIN (1B)—A desiccated extract of orchitic substance in 5-gr. tabloids, each of which represents the amount of fresh tissue indicated. Dose: One or more t.i.d. *(Burroughs Wellcome & Co.)*

HOMBREOL (1A)—A solution of the male sex hormone in olive-oil for intramuscular injection, physiologically standardized, each ampule containing 4 "cockscomb units." As a general and sexual tonic. Dose: 1 or more ampules daily or every other day. *(Degewop Gesellschaft A.-G., Berlin.)*

LYDIN* (1B)—A concentrate from the interstitial cells of Leydig from bovine testes, each 5-gr. capsule containing the active principle obtained from 7 Gm. (108 gr.) of fresh Leydig cells. To this is added the "anterior-pituitary-like gonad-stimulating hormone" (Plagonin) from 20 gr. of fresh placenta, plus a suitable dose of the fat-soluble antisterility vitamin *E*. Administered to capons in sufficient doses, the Leydig cell ingredient is capable of replacing the missing hormone to such a degree that growth is produced in the visible secondary sex tissues, comb, and wattles. Dose: 1 or 2 capsules at meals and at bedtime.

LYDIN SOLUTION, STANDARDIZED* (1A)—A stable, potent solution, each cubic centimeter representing the essential male sex principle in 227 Gm. of fresh bovine interstitial cells of Leydig standardized by its growth-stimulating effect upon the combs of capons. Usual dose: 1 cc. intramuscularly daily or every other day, with 1 capsule q.i.d.

ORCHIC EXTRACT (1B)—The desiccated, defatted parenchymatous tissue of the testes of bulls, one part of which is equivalent to nine parts of fresh orchic substance. In powder, tablets, or capsules. Also in solution, each cubic centimeter containing the soluble extract in 27 gr. of fresh tissue. Dose: From 5 to 15 gr. t.i.d. and/or 1 cc. daily or every other day.

SPERMIN—A solution of the crystalline chemical substance, spermin, $C_{10}H_{26}N_4$. Available in ampules *pro injectione* (1 cc. daily) and *in essentia* for oral use (30 min. t.i.d.). *(v. Poehl and Söhne, Berlin).*

TESTIKULIN (1B)—A glycerin extract of fresh testicular substance for oral administration. Dose: From 30 to 60 min. t.i.d. *(Schering-Kahlbaum A.-G., Berlin.)*

12. THE HEART

Heart Extracts—Other Muscle Extracts—Cannon's Sympathin—Myocardin—Therapeutic Prospects—Extracts of Heart and Other Muscles.*

ACCORDING TO Sajous (1916) "the cause of the rhythmic beat of the heart lies within the heart itself." This great endocrinologist had more vision than his fellows, and predicted many an advance in endocrinology before it materialized. It seems that he was right in this matter of the heart hormone too.

Some years later, R. Alexander Bate, of Louisville, Kentucky (*Am. Med.*, Feb., 1922, xxviii, p. 94), called attention to the facts that the heart-beat has never been produced experimentally by stimulation of nerves supplying the heart, and that the dog's heart with all its nerve connections severed survived eleven months (Hoover). He referred to experiments demonstrating that a strip of muscle from the ventricle of the tortoise has been made to contract when suspended in the atmospheric oxygen, "hence, it appears that oxygen liberates autacoids, *i.e.*, hormones and chalones, or cardiac secretions, which in their turn cause the mechanical action of the heart—rhythmical muscular contractions." Bate then quotes Sajous' statement given above, and adds: "The 'granules' of Sajous, or the nucleoproteid principle of the heart, is probably a specific hormone."

HEART EXTRACTS—J. Demoor, of Brussels (*Arch. internat. de physiol.*, 1922-1923, xx, pp. 29, 446), was the first to show that aqueous extracts of the right auricle of the dog's heart exert a pulse-producing, pulse-accelerating, and pulse-stimulating effect on the corresponding portion of the rabbit's heart. He has also shown (*ibid.*, 1924, xxiii, p. 124) that the extracts of the Keith-Flack sinus nodes in particular (the site of formation of the normal heart stimuli) act in the same manner.

In 1924, L. Haberlandt, of Innsbruck, Austria (*Klin. Wchnschr.*, Sept. 2, 1924, iii, p. 1631; and *Wien. klin. Wchnschr.*, Nov. 26, 1925, xxxviii, p. 1280), working independently, demonstrated a stimulating substance in the uppermost venous portion of the frog's heart (sinus venosus), which, because of its origin at the site of origin of the cardiac beat and its manner of action, he recognized as the exciting factor in cardiac activity. He therefore designated it as the automatic substance, or the hormone of cardiac action, or the heart hormone.

The view that the heart-beat is regulated by a humoral substance, produced chiefly in the sino-auricular node and right auricle, has been developed by Haberlandt, who obtained with the frog heart similar augmenting and

accelerating effects with extracts of sinus and right auricle. He called this active principle the "sinus hormone," but later he found it also in the auricle, auriculo-ventricular ring, and base of the ventricle. This he believes to be the normal stimulus for the spontaneous heart-beat, the constant excitation producing a rhythmic effect owing to the refractory period of cardiac muscle (*Wien. klin. Wchnschr.*, Nov. 4, 1926, xxxix, p. 1297).

Haberlandt reported some researches with preparations obtained from frogs' hearts in *Klinische Wochenschrift* (April 9, 1926, v, p. 654). One extract, made with alcohol, is claimed to contain a heart hormone. It has been proved possible by its use actually to excite a heart to contract after it has entirely ceased functioning. It is claimed also to increase the rate and the strength of the pulsations. In a later issue of the same journal (Aug. 13, 1926, v, p. 1522), Haberlandt claims that the alcoholic extract retains its potency as long as twenty-five days; extracts prepared with ether are inactive, the hormone being insoluble in ether; consequently, it cannot be lipoid in nature. Aqueous extracts of heart muscle are dialyzable, which suggests that its composition is not high-molecular. The heart hormone is thermostable, an apparently characteristic property of many hormones.

According to Haberlandt's quite extensive observations, the effects that this substance exerts on the heart action are analogous to those of adrenin but not identical with them, because, in contrast to the vasoconstricting action of adrenin, the heart hormone has a vasodilating action.

In the opinion of the Dutch workers, H. Zwaardemaker and P. Arons (*Nederl. Tijdschr. v. Geneesk.*, Sept. 10, 1927, ii, p. 1111), the heart hormone is formed from an unknown mother substance contained in the heart, skeletal muscle, and blood. By means of radium irradiation of frogs' hearts stopped by potassium deprivation, Zwaardemaker calls attention to the production of "irradiation substances" that can induce the reappearance of the cardiac beat. These substances apparently are identical with the cardiac hormone, and were called "cardiac automatics." The nodal tissue of the heart has a special affinity for this substance (which these authors call "automatine") and contains it in higher concentration.

In France, G. Katz and E. Leibenson (*Presse méd.*, July 28, 1928, xxxvi, p. 951) also have succeeded in extracting from the cardiovascular apparatus and endocrine glands of warm-blooded animals, substances that provoke cardiac contractions in cold-blooded animals.

The nature of this research aroused considerable opposition, but it is rare for any announcement in this field to fail to do so. The first criticism of Haberlandt's work was naturally that his concentrate was only a protein

derivative like histamine. For example, R. Rigler and F. Tiemann, of the University of Vienna (*Klin. Wchnschr.*, March 18, 1928, vii, p. 553), demonstrated that the effect of "the alleged heart hormone" on the blood-pressure and on the uterine wall is like that of histamine, and that both produce anaphylaxis-like effects in guinea-pigs. They also showed that the physical and chemical properties of this stimulating substance correspond to those of histamine. Prior to this work, W. Weichardt, of Erlangen (*Klin. Wchnschr.*, Aug. 13, 1927, vi, p. 1555), had advanced the idea that Haberlandt's heart hormone was simply an example of his general hypothesis regarding the function-increasing action of cleavage products. The possibility that histamine might be responsible for a part of this activity was considered, for histamine is often present in animal extracts. In a communication to *Pfluger's Archiv* (*Arch. f. d. ges. Physiol.*, 1929, cci, p. 576), however, Haberlandt states that his heart hormone preparation was still active after being rendered completely free from histamine.

Later, certain experiments by V. Pawlenko in Germany (*Centralbl. f. allg. Path. u. path. Anat.*, 1929, xlv, p. 272) convinced him that a specific heart hormone does not exist. He found that the skeletal musculature and a simple Ringer-Locke solution contain albumin traces. It was believed that albumoses, peptones, and amino-acids in definite concentration and mixture influence the heart in quite the same way as does the substance designated "heart hormone" by Haberlandt.

G. Zuelzer, of Berlin, who prepared "Eutonon" from the liver, reiterates (1929) his doubt of the hormone nature of Haberlandt's principle. At the Vienna Conference for Internal Medicine, it was said that Haberlandt's ideas were hard to prove because he used the frog for his experiments, and many chemical substances have the same effect on the frog heart as the heart substance of Haberlandt. He suggested that experiments on mammals should be undertaken before convincing proof could be obtained.

There is very little record of research along these lines in this country. About the only report is that of Enid T. Oppenheimer, of New York (*Am. Jour. Physiol.*, Nov., 1929, xc, p. 656), who repeated Haberlandt's experiments and found that her heart muscle extracts frequently contained a substance having a stimulating action on the heart, which, however, was often followed by a toxic action. Similar effects were obtained from extracts of other tissues, suggesting that this substance, whatever it may be, is not a specific heart hormone.

A heart-stimulating substance was found in urine by E. K. Frey and H. Kraut, of Berlin (*Ztschr. f. physiol. Chem.*, 1926, clvii, p. 32); also by

Frey and Kraut with E. Bauer (*ibid.*, 1928, clxxv, p. 97). This substance increases the amplitude of the beat, often causing acceleration of rhythm. The authors are of the opinion, however, that the active substance is not identical with histamine, because it acts in smaller concentration and does not produce the enlargement of the liver that histamine does. This principle is now believed to originate in the pancreas, and is considered further in that connection (15). These two principles, the cardiac heart hormone and the pancreatic circulatory hormone are quite dissimilar and must not be confused. About this same time, G. Zuelzer, of Berlin, produced Eutonon, an extract from liver with a similar effect, to which attention is paid in Chapter 13.

OTHER MUSCLE EXTRACTS—The subject has been complicated still further by announcements from several sources of the separation from voluntary muscle of a principle that has clinical potentialities quite similar to those of the heart extract, especially a symptomatic beneficial effect in angina pectoris.

Because the symptoms of intermittent claudication seem to have a close relationship to those of angina pectoris, M. S. Schwartzman, of London (*Brit. Med. Jour.*, May 10, 1930, i, p. 855), used muscle extract with successful results. In fact, five cases of thrombo-angiitis obliterans were recently demonstrated by Schwartzman before the Royal Society of Medicine, all of which had improved under treatment with muscle extract. The author suggests (*ibid.*, March 21, 1931, i, p. 492) that undoubtedly there are, particularly in an active muscle, some substances (metabolites?) that are partly responsible for the increased blood supply required for exercise.

"It is likely," he says, "that these substances form the active principle of the muscle extract. Not much can be said yet about their chemical nature. The extract contains but very little histamine, if any. The substances are not identical with choline, and the depressor action is not counteracted by atropine. They may contain adenosine, as was recently suggested, but physiological experiments indicate that they are not likely to be identical with it."

However, J. S. Schwarzmann, of Odessa (*München. med. Wchnschr.*, Aug. 9, 1929, lxxvi, p. 1329), had previously treated seventy-three cases of angina pectoris with subcutaneous injections of an extract from the skeletal muscles of calves, called "Myol," with good results.

K. Fahrenkamp and H. Schneider, of Stuttgart (*Med. Klin.*, Jan. 10, 1930, xxvi, p. 48), made some comparative clinical studies of an extract of heart muscle (Haberlandt), which in the meantime had been made generally available as "Hormocardiol," and an extract of voluntary muscle

free from albumin, histamine, and epinephrine. The latter produces identically the same effects as Haberlandt's heart muscle extract. Both cause marked slowing of the ventricular rate—in fibrillating patients and in those with sinus rhythm when the extract is administered orally under the influence of digitalis. The most satisfactory results were obtained in angina pectoris. Both extracts controlled the seizures almost completely, but, if administered to patients under the influence of digitalis, the extract produced symptoms of angina pectoris. Apparently, however, this is not the case with the heart hormone.

It might be added here that A. N. Drury and A. Szent-Györgyi, of Cambridge University (*Jour. Physiol.*, Nov., 1929, lxviii, p. 213), recorded the isolation from muscle and other tissues of a substance which, from its clinical effects, they considered as identical with adenylic acid. Besides having several reactions upon the whole animal, it was an arterial dilator affecting also the coronary arteries. Research on the rabbit heart showed that this was an efficient coronary dilator. These workers also found that adenosine, prepared from yeast nucleic acid, had properties identical with those of muscle adenylic acid.

CANNON'S SYMPATHIN—W. B. Cannon and Z. M. Bacq, of Harvard (*Am. Jour. Physiol.*, Feb., 1931, xcvi, p. 392), recently described a new hormone to the Yale Medical Society. This discovery came about as a result of an attempt to confirm the opinion that there are heart stimulants like adrenin in other parts of the vegetative system. They cut practically every sympathetic nerve in the body of a cat, particularly the nerves running to the heart and to every organ known to produce a hormone. They shook the cat's fore paws and then its head, but there was no reaction either time. When the hind quarters were shaken, however, the heart, whose nerves had been disconnected, started to beat faster. Then they clamped the arteries and veins connecting the heart and the abdominal viscera, damming the blood stream, and the heart returned to normal. Releasing the pressure on the veins and arteries, they again shook the cat's hind quarters, and again the heart began to beat faster than normal. Cannon concluded that the movements of the cat's lower muscles manufacture something that stimulates the heart; that is, a hormone similar to adrenin. This new muscle hormone is called "sympathin."

MYOCARDIN*—A concentrate from beef heart muscle has been in use for several years under the name "Myocardin." It is not the Haberlandt active principle, although it may contain it; nor is it based on the German reports, but on work done in France with a similar desiccated cardiac extract.

Comparatively speaking, Myocardin is a crude, unstandardized product, yet many physicians claim that it has therapeutic value in myocarditis and myocardial insufficiency. There are no acceptable explanations as to how this empirical product acts.

Following its administration there may or may not be symptomatic improvement. It is as hard to explain how the good results are secured, as it is to tell why the remedy fails in a given case. Some of the clinical possibilities of Myocardin are referred to in Chapter 45.

After these data were assembled, attention was called to a report by Haberlandt (abstr. in *Am. Med.*, May, 1928, xxiii, p. 412) in which he seems to have reverted from the use of the isolated active principle to a simpler heart extract which is given by mouth.

THERAPEUTIC PROSPECTS—It is evident that out of all this research one or more new therapeutic agents will emerge. Already half a dozen or more are on the market—all in Europe, with one exception. Two brief reviews are available, both from the *Lancet*. It is necessary to consider the subject from the clinical standpoint, for here we have four sources of what may turn out to be the same thing. As the cardiovascular potentialities are discussed in the section on Endocrine Therapeutics (45), it will suffice for the moment to read what the editor of the *Lancet* (March, 7, 1931, ccxx, p. 533) has to say:

"G. Zuelzer has prepared an extract from the liver, named eutonon, which has claims to be regarded as a cardiac 'tonic,' and there are numerous other tissue extracts in use, such as angioxyl (from the pancreas), myoston (from muscle), kallikrein (from urine), and lately lacarnol (from striped muscle).

"Similar claims are made for these preparations as for the original heart preparation (hormocardiol) of Haberlandt; in general they are held to increase the rate and strength of the pulse, to dilate vessels, especially the coronary arteries, and to restore a regular rhythm in experimental auricular fibrillation. Needless to say, such properties would be very valuable in clinical practice, and it is now possible to review the results obtained in a fairly large series of cases, mostly in continental clinics. The extracts have been employed mainly for angina pectoris, endarteritis obliterans, cardiac failure, and high blood-pressure."

From the same source comes some later news indicating that the subject has the attention of the British Ministry of Health. Here is another brief item from the *Lancet* (July 4, 1931, ccxxi, p. 27):

"The claims made for the value of extracts of muscle and other tissues in circulatory disorders are being put to further test. U. S. v. Euler and J. A. Gaddum, working at the Medical Research Institute, have studied the depressor and vasodilating action of certain tissue extracts, and the possible

nature of such depressor substances. They conclude that at least five different types of such vasodilator substances may occur in tissue extracts. These are: (1) histamine, (2) choline and choline esters, (3) substances allied to adenosine, (4) and (5) two hitherto unidentified substances not belonging to any of the first three groups. One such substance, which has been called kallikrein, is present in urine and pancreas; the other, v. Euler and Gaddum have prepared by acid-alcohol extraction from a number of organs such as small intestine, brain, stomach, and bladder. Experimentally it is found that adenosine and its allies slow the heart, whilst kallikrein accelerates it; all these substances appear to lower appreciably the arterial blood-pressure in laboratory animals.

"Clinical trials of such tissue extracts—'circulation hormones' has been suggested as a name for them—have been extensively carried out on the Continent. . . . The conditions for which these preparations have been principally used have been angina pectoris, high blood-pressure, arteriosclerosis, and peripheral vascular disorders such as Raynaud's disease."

EXTRACTS OF HEART AND OTHER MUSCLES

AUTOMATINE (3)—A principle still more or less hypothetical, formed from an unknown mother substance contained in the heart, skeletal muscle, and blood. Zwaardemaker believes that the nodal tissue of the heart has a special affinity for this substance and contains it in a higher concentration.

HORMOCARDIOL (2)—A solution containing Haberlandt's heart hormone which, in suitable concentrations on a suitable sensitive heart, produces a pulse-inciting and pulse-accelerating effect. *(I. G. Farbenindustrie A.-G., Berlin.)*

LACARNOL (1B)—An extract of the skeletal muscle of warm-blooded animals. It is of neutral to slightly alkaline reaction and is thermostable. The potassium- and calcium-ion content of Lacarnol produces no demonstrable pharmacologic effect. Used chiefly in angina pectoris and related vascular disorders. Vials of 20 cc. Dose: 20 min. two or three times a day. *(Bayer, Meister-Lucius.)*

MYOCARDIN* (1B)—A desiccated beef heart muscle extract. Used in myocarditis, angina, and allied heart disorders. Dose: From one to three 5-gr. capsules three times a day.

13. THE LIVER

A Source of Many Remedies—The Bile Salts—The Circulatory Hormone: Eutonon — The Detoxicative Hormone: Anabolin, Heparmone, Yakriton—The Hemopoietic Hormone, or Hemopoietin—Heparnucleate,* Liver Extract No. 343, etc.—Parenteral Therapy—Liver Extracts.*

THE DISCOVERY of a potent remedy from the liver, as the editor of the *Lancet* expresses it, was "one of the most sensational episodes in the history of medicine" (*Lancet,* April 28, 1928, ccxiv, p. 863). As has been stated many times, this sensational episode has done even more to establish confidence in organotherapy than the equally spectacular production of insulin.

A SOURCE OF MANY REMEDIES—The liver has been appreciated as a source of remedial agents for many hundreds of years. Some time ago I published an article entitled "Twelve Hundred Years of Liver Therapy" (*Clin. Med. and Surg.,* Aug., 1928, xxxv, p. 586). A part of the introduction to this article is appropriate here:

"Record regarding the medicinal uses of liver among the ancients was made as long as twelve hundred years ago by Paulus Ægineta, the great compiler of the seventh century, who says in his last book: 'Hepar, the Liver: if that of a mad dog be roasted and eaten, it is said to relieve those who have been bitten by him. The sanies of a boiled goat's liver relieves nyctalopia when injected into the eye. They also direct the vapour of it when boiling to be received into the eyes, and also to be eaten. They say that it rests epileptics if eaten, and that the liver of the buck-goat does the same. The liver of a lizard when put into carious teeth relieves the pain. That of the wolf is added to the hepatic medicine prepared from eupatorium. The liver of an ass when roasted is of use to epileptics when eaten fasting. That of a bear when dried in its fresh state and triturated with wine is drunk for the bites of reptiles. The liver of the cormorant, when dried and taken in a draught, makes calculi to be discharged.'

"To-day, this sounds as absurd to us as a statement of our present knowledge would have sounded as little as ten years ago. For example, what would the reader have said to the following statement, if it had been made a few years ago?

" 'Hepar, the Liver: if the liver of calves be chopped and eaten in a soup or purée or slightly cooked, it will cure pernicious anemia, and many cases are on record where a red-cell count of one million and less has been changed to five million or more in so short a time as a month or six weeks. . . . Another principle also extracted from the liver may be given with great success in the treatment of certain cases of high blood-pressure. . . . It is active largely through the influence it exerts upon the power of the liver to destroy poisons and particularly those which have a pressor influence.'

"Such claims would have been laughed at a few years ago, just as many other organotherapeutic claims have been ridiculed. . . . The present-day opinion of organotherapy is vastly different from what it was only ten years ago. The impossible has become a reality and the absurd is welcomed with delight; for, whoever thought that a diet of liver would be of benefit in so incurable a disease as pernicious anemia! For hundreds of years the literature has contained occasional references to the therapeutic possibilities of liver and biliary products, and many other recommendations equally as strange as those offered by Ægineta may be found. Those among renowned physicians of antiquity who have written in favor of liver therapy are Galen, Oribasius, and Vesalius, though their recommendations are read with as much reservation in these days as are more recently written statements about organotherapeutic possibilities.

"It was the famous French physiologist, Claude Bernard, who first suggested that the liver might also produce an internal secretion. In fact, his experimental demonstration of the glycogenic function of the liver was one of the principal foundation-stones on which are builded the twin essentials of metabolism and endocrinology. Claude Bernard spoke of the liver as a distinct endocrine organ and it happened that in this consideration of the endocrine function of the liver he used, for the first time, that phrase now so common—'internal secretion.'"

THE BILE SALTS—The most widely used of the liver products are the bile salts. More than three thousand years ago, the inspissated bile of the hedgehog, killed during a certain quarter of the moon, was recommended for indigestion; and ox-gall has long been a useful remedy. This centuries-old method of using the contents of the gall-bladder as a remedy has recently come into greater vogue than ever before, and it is now known that these bile salts serve as a means of encouraging bile production on the part of the liver, thereby exerting a very beneficial effect on alimentary conditions.

We now know that the principal therapeutic value of bile lies in its salts, sodium taurocholate and sodium glycocholate. These are not hormone remedies, but they are essentially organotherapeutic products. It is interesting to note how the bile renders its service. Mixing with the half-digested food in the upper intestine, the bile serves three purposes: (1) It neutralizes the acid chyme to prepare it for pancreatic digestion; (2) it antagonizes the growth of the alimentary putrefactive organisms; and (3) it apparently has a definite effect on the chemistry in the bowel itself, particularly in so far as the production of mucus is concerned. After these duties have been performed, the bile salts are absorbed with the food, enter the portal vein, and are returned to the liver, where they are used again. Biliary organotherapy, then, is a means of increasing the amount of bile salts reaching the liver, where they are made over into bile.

Obviously, the principal indication for organotherapy with bile salts is biliary insufficiency, but it is of symptomatic use also in functional liver insufficiency, intestinal stasis, gall-stones, duodenal indigestion, chronic nutritional disorders such as tuberculosis, in which hepatobiliary function is especially important, and in chronic hepatic disease.

This form of therapy exerts a quite remarkable mechanical effect in conditions in which biliary stasis is a detriment. This has been proved a number of times when post-operative drainage had been instituted. The administration of bile salts to such patients has trebled the amount of bile passed through the drainage tube. Naturally, in chronic gall-bladder infections, and even when gall-stones are suspected, the increase in the amount and flow of the bile is mechanically advantageous.

Physicians who have come to depend on biliary stimulation and who use it frequently in a wide range of disorders, report by-effects on certain toxic difficulties such as hypertension, heart disease, angina, etc. These make one believe that, with the improved biliary service and consequent modification of hepatobiliary stasis, there is also an increased hepatic hormone production with benefit comparable with that claimed from the use of Anabolin* (*q.v.*).

Various forms of bile are easily obtainable, the best products being the repurified bile salts, not just desiccated ox-gall or the chemically purified salts. The dose ranges from 3 to 30 gr., and it is an advantage to give it in the step-ladder fashion, gradually increasing the amount until the presence of free bile in the stools is evidence that the liver is working faster than is necessary. When the yellowish-green bile is found floating on the water of the toilet, treatment is omitted for a few days, then commenced again. Usually, it is not best to give bile salts with cathartics, for the catharsis caused by the latter will interfere with the generous and prolonged dosage of the bile salts that is needed to reestablish the hepatobiliary functions (104).

THE CIRCULATORY HORMONE: EUTONON—We shall shortly see that there is a remarkable and potent circulatory hormone obtainable from the pancreas (15). A somewhat similar principle, or a product with a similar action, is to be found in certain liver fractions, at least so we are assured by G. Zuelzer, of Berlin, who has a record of many accomplishments in endocrine biochemistry.

Zuelzer's liver principle, known as "Eutonon," is now being used in anginoid conditions related to heart-muscle weakness. It is claimed that through humoral influences this liver principle raises the reserve power of the cardiac muscle. Many of the clinical reports refer to its use in the cardiac incidents of training, serious infections and infectious diseases, and age.

THE DETOXICATIVE HORMONE: ANABOLIN,* HEPARMONE, YAKRITON—The profession is indebted to William J. Macdonald, of St. Catharines, Ontario, for directing attention to this subject. Macdonald, especially interested in the liver as an organ of defense, conceived the idea that in view of the remarkable detoxicative powers of this organ it might be possible in some way to utilize it in the prophylaxis of cancer, and perhaps even to develop a therapeutic procedure in its control (*Proc. Soc. Exper. Biol. and Med.*, 1924-1925, xxii, p. 483). These studies led to a consideration of the metabolism of uric acid and carcinoma. It was found that J. A. Killian and L. Kast, of New York (*Arch. Int. Med.*, Dec., 1921, xxviii, p. 813), had shown that in 80 per cent. of the cases of internal cancer studied by them there was a definite increase in the blood uric acid. Further, it has been found by F. C. Mann and T. B. Magath, of Rochester, Minnesota (*Tr. Sect. Path. and Physiol. Am. Med. Assn.*, 1921, p. 29), that death following experimental hepatectomy was preceded by a speedy rise in the blood uric acid.

Macdonald's conclusions, strengthened by his own experimental work and fortified by these reports and others, culminated, as he expresses it (*Can. Med. Assn. Jour.*, July, 1925, xv, p. 697),

". . . in an hypothesis, the main point in which was that the liver secreted some substance which played an important part in the regulation of blood uric acid, and that if such substance could be recovered, internal carcinoma might be controlled."

In the early experiments in 1923-1924 some notable depressor effects followed Macdonald's use of his trial liver extracts. These undoubtedly were due partly to the presence of the protein breakdown product, histamine.

The complex phases of purification of this extract and its standardization were attacked by A. A. James and N. B. Laughton, of the Western Ontario Medical School, in London, Ontario, and later in the Department of Physiology at Toronto. Macdonald and his associates (*Proc. Soc. Exper. Biol. and Med.*, 1924-1925, xxii, p. 483) early summarized the matter thus:

"1. An extract of the liver has been obtained which possesses the property of reducing to a certain extent essential arterial hypertension.

"2. It is quite possible—even probable—that the active principle of this extract may be recovered from other body organs and tissues.

"3. This extract contains no protein.

"4. This extract contains no peptone.

"5. This extract contains histamine in relatively small quantities, and cholin in relatively large quantities.

"6. It is quite possible that the effect produced by a proper combination of these two substances may be responsible for the lowering of pressures noted in both laboratory animals and in clinical cases.

"7. It is more probable, however, that because of the much greater effect produced by a given quantity of the extract than can possibly be obtained by the injection of even many times the quantity of histamine and cholin contained in the said quantity of extract, the result is due to an unknown substance, or that this unknown substance may activate either the histamine, cholin, or both.

"8. Intramuscular injection is much more efficacious than intravenous.

"9. The extract is much more effective in hypertensive than in normal cases.

"10. We have as yet no method of determining our selection of cases for treatment.

"11. Whereas our method of assaying this present extract in units is definite, we have as yet no method of determining the dosage in units to any given case."

Meantime, Ralph H. Major, of Kansas City, was investigating the relation of the guanidine bases to blood-pressure (*Bull. Johns Hopkins Hosp.*, May, 1924, xxxv, p. 140) and seeking means of controlling the hypertension believed to be caused by guanidine (*ibid.*, May, 1925, xxxvi, p. 357). His first article on the effects of hepatic extracts on high blood-pressure was published in the middle of 1925 (*Jour. Am. Med. Assn.*, July 25, 1925, lxxxv, p. 251). From that time an increasing number of papers were published by various writers, all confirming first one point and then another about extracts that act on and through the liver, and which are capable of reducing the blood-pressure both experimentally and clinically.

Eventually the interests of Major, Macdonald, and Scott were combined, and a liver product known as "Heparmone" was made available in 1927. There are several clinical reports of its utility in hypertension, eclampsia, etc.

A most interesting series of reports was published in Japan by Akira Sato and his associates in the University of Tohoku at Sendai (*Tohoku Jour. Exper. Med.*, Dec., 1926, viii, p. 232 *et seq.*). From these papers it is clear that a liver extract may be prepared which contains a potent detoxicating principle, the experiments with which were conclusive. Sato first determined the amounts of various poisons—ammonium chloride, histamine, chloroform, etc.—that would cause convulsions in rabbits of given weight in fifteen minutes, and death thereafter. This was not simple, and more than fifteen hundred rabbits were needed for the series of experiments. Having determined as nearly as possible the lethal doses for the different rabbits, suitable amounts of the liver extract were given to protect them from the known-to-be-poisonous dose. Sato and his associates found that their product was capable of so raising the capacity of the liver to destroy poisons of this nature that the rabbits suffered comparatively little. It was possible for them to work out a "rabbit ammonia unit" of potency whereby they measure the protective influence of this liver principle. As a result of these experiments,

Hiroshi Sakurada and Akira Sato (*Tohoku Jour. Exper. Med.*, June, 1927, ix, p. 66) consider this active principle to be a true hormone—thus:

"Yakriton is not only the ammonia-regulating principle, but also the urea-regulating principle. It is thus made more probable that Yakriton should, as already predicted in the first report of these studies, represent the detoxicating hormone of the liver."

Sato's product has since been made available in Japan as "Yakriton," and the clinical recommendations for its use seem to be limited to the more definite liver diseases and conditions in which dye excretion is impaired.

In July, 1925, after many failures, "a depressor liver extract" was prepared in stable, standardizable form. This substance was believed to be the active principle previously mentioned by W. J. Macdonald, and was named "Anabolin"* because it was believed that its effects were brought about by the enhancement of the anabolism by the liver.

This product is a residue obtained by fractional alcoholic extraction of fresh liver tissue, and is freed from all other depressor substances except a trace of histamine (0.0001 Gm. per cc.), which is sufficient to cause a chemical reaction indicating its presence but quite insufficient to be responsible for the marked physiological potency for which Anabolin is now noted.

The physiological activity of Anabolin is uniform, and its effect on the blood-pressure is so easily determined that it serves as an acceptable means of assaying the product. This endocrine principle is physiologically standardized to bring about its typical depressor reaction, which is accurately recorded by means of the kymograph. One cc. of the "standard" solution of Anabolin is capable of reducing the blood-pressure of a normal 10-kg. dog by 12 mm. Hg. This method is dependable, the records of various tests being compared and measured with great exactness so that the activity and stability of various batches may be definitely established.

When this product was finally made available to the profession (October, 1925) it was offered as a depressor substance, and its influence on the blood-pressure was not attributed to the marked influence on hepatic detoxication that it is now known to exert. This was natural in view of Macdonald's reports and the very obvious effects of Anabolin on the blood-pressure of normal dogs. However, the clinical value, as well as the experimental effects, is now explained in a comparatively simple way. The immediate depressor effect of this extract is brought about in two distinct ways:

1. It causes an increase in the circulation of the liver and alimentary organs. This is quite in harmony with the law of hormone activity, for it is well known that endocrine principles bring about a good share of their catalytic stimulating effects by first causing hyperemia of the organs that

correspond to those from which they are made. (Injections of folliculin—the ovarian hormone—or of secretin show most conclusively a remarkable stimulation of the local circulation with consequent hyperemia of the ovaries and adnexa, on the one hand, and of the duodenal mucosa, on the other.) This hyperemia of so large an organ as the liver may suffice to cause the initial and temporary drop in pressure by purely mechanical means. Simultaneously, this circulatory change prepares the way for better functioning on the part of the structures thus affected. This explains the second response:

2. Hepatic detoxicative activity is encouraged, particularly that function sometimes called anabolism, whereby the toxic protein wastes are built up into the non-toxic substance, urea, which is eliminated through the kidneys, and constitutes about 90 per cent. of the excretion of nitrogenous wastes.

This explains the preliminary depressor effect, as well as the ultimate influences of this remarkable endocrine catalyst; furthermore, these effects may be put to excellent clinical use in certain circumstances, as will be seen in the consideration of hypertension (45) and eclampsia (84). In conclusion, a quotation may be made from an article by T. L. Althausen, W. J. Kerr, and T. C. Burnett (*Am. Jour. Med. Sc.,* March, 1929, clxxvii, p. 398):

"1. The treatment of hypertension with liver extract brings about a considerable lowering of the blood-pressure and affords complete or marked symptomatic relief in a majority of cases.

"2. Hypertension cases of known duration under two years, without marked arteriosclerosis, and showing no fixation of specific gravity in the Mosenthal test, offer the best prognosis.

"3. The most important objective of the present work from the point of view of the investigator is to determine by observations over a long period of time whether cardiovascular-renal damage can be arrested or prevented by artificial lowering of high blood-pressure in hypertension."

THE HEMOPOIETIC HORMONE, OR HEMOPOIETIN—An active hematinic fraction may be separated from fresh liver, thus confirming the therapeutic potentialities made clear in the research work of G. H. Whipple and his coworkers in the University of California in 1920 (*Am. Jour. Physiol.,* Sept., 1920, liii, p. 236). In experiments on dogs with anemia caused by repeated bleedings they showed that the blood-picture could be reestablished most quickly and completely by feeding fresh liver.

It was not until 1926 that the announcement was made by G. R. Minot and W. P. Murphy, of Harvard University, that they had been successful in causing marked remissions in pernicious anemia by feeding calves' liver (40). The astonishing therapeutic accomplishments of liver therapy are outlined in many reports, but opinions as to how this effect is brought about

are not so numerous. It is obvious that the liver fraction contains a certain hemopoietic principle, or hemopoietin, which directly or indirectly hastens the production rate of the reticulocytes. Some writers, especially those in Germany, believe that this principle is a true hormone. Others are convinced that no matter how it works, the philosophy of catalytic action is the only way whereby the marked reticulocytosis can be explained.

Certain it is that the capacity of this hemopoietin to cause reticulocytosis is spectacular, and the prospects appear to be better the lower the red blood-count. Increases of 1,000,000 red cells per cubic millimeter following its administration for a fortnight are not unusual. A little mathematics will impress this mightily: There are 1000 cubic millimeters in a cubic centimeter and 1,000,000 in a liter, hence an increase such as the foregoing means that 1,000,000 times 1,000,000 new cells are produced for every liter of blood. Since there are from 6 to 7 liters of blood in an average man, this means that the administration of a few centigrams of the liver hemopoietin can bring into existence 6,000,000,000,000 *new* cells in ten days or two weeks! Incidentally, a record is given elsewhere (40) of a case treated in this manner for less than a month with a gain of 3,000,000 red cells per cubic millimeter, or a gain of 18,000,000,000,000 new blood-cells.

Apparently these reticulocytes are increased not only in number but also in utility, and the majority of them quickly become non-nucleated or full-grown red blood-cells. It is noted frequently, however, that the hemoglobin content does not increase simultaneously with the red cells; in fact, improvement following the use of preparations of this nature occurs in three steps and in the order mentioned: (1) reticulocytosis, (2) maturation of the reticulocytes with the relative increase in the number of true mature red blood-cells, and (3) increase in the hemoglobin index.

Since 1926 a large amount of research work has been done with liver therapy and, as one can judge quite accurately the responses to various products, it is now the rule to give liver therapy in conjunction with other suitable cooperative measures. Attention will be called to the discoveries in the University of Oregon with regard to the cooperative value of sodium nucleate with liver extract and the explanations given for the improvement of this idea by substituting the nucleate of iron (40). This formula, known as Heparnucleate,* does not increase the rate of reticulocytosis more rapidly than liver products containing no added iron, but it obviously hastens the increase in the hemoglobin content which, of course, is equally necessary.

As a result of the researches of E. B. Hart and H. Steenbock at the University of Wisconsin, it has been found that, when iron is administered,

it largely fails in the formation of hemoglobin unless copper is also present. Fresh liver contains both copper and iron, while liver extract does not contain such a large proportion of these metals. It seems that the added metals are indispensable for the utilization of iron in building up the structure of the hemoglobin molecule. (See *Jour. Biol. Chem.*, May, 1928, lxxvii, pp. 769, 777, 797; July, 1929, lxxxiii, pp. 21, 27, 243, 251; Oct., 1929, lxxxiv, p. 115.) This may explain an experience that is referred to elsewhere (40), which indicates that a half pound of fresh liver taken once a week supplements very materially the hemopoietic effect of liver therapy in pernicious anemia.

HEPARNUCLEATE,* LIVER EXTRACT NO. 343, ETC.—When liver therapy was first recommended in anemia, two misunderstandings were frequently overemphasized. First, all the early reports referred to liver *feeding,* and the then available liver extracts were of practically no service. Particularly was this true of Anabolin,* which was then (1925-1926) in its clinical infancy. It was used and judged by its effect *in anemia* and, unfortunately, conclusions were drawn that were unwarranted—exactly as conclusions about adrenal therapy in hypoadrenia were judged from the point of view of adrenalin, when, in fact, hypoadrenia is not adrenalin insufficiency at all.

Then liver extract was perfected and the "hemopoietic hormone" was separated. In the early reports it was claimed repeatedly that this new measure was a cure for pernicious anemia. Even more often it was stated that liver therapy was of value only in true pernicious anemia, *i.e.,* that it was of no value in secondary anemia. The eminence of those responsible for these misstatements impressed them the more. It is a tremendous satisfaction to have been aware of the truth before it was generally accepted; I exult in the decisively demonstrated fact that liver therapy may be of the greatest value *in all serious anemias,* although, of course, it is regrettable that it does not cure pernicious anemia.

Several products have been perfected in this country, Liver Extract No. 343 having been sponsored by the Committee on Pernicious Anemia of the Harvard Medical School. This is the fraction first isolated by Cohn, Minot, Alles, and Salter in 1927, which contains the major portion of the material in whole liver that was found capable of causing such marked remissions in pernicious anemia. The process of preparation is outlined as follows (*Jour. Am. Med. Assn.,* Feb. 4, 1928, xc, p. 385):

"Livers from edible animals are ground directly into water, and the mixture adjusted to the isoelectric point (approximately pH 5 to pH 6). The mixture is then heated to coagulate protein (approximately 80° C.); stirred for thirty minutes, and filtered. The filtrate is reduced in vacuum to a small volume and enough 95 per cent. alcohol added to produce a con-

centration of 70 per cent. The precipitate which is formed is discarded and the filtrate reduced to a small volume; added to absolute alcohol and the precipitate separated, dried in vacuum, and powdered."

This extract is "standardized" by clinical testing in a patient with primary pernicious anemia whose red blood-count is 2,500,000 or below. The rate of reticulocytosis caused by the extract is used as the measure of its potency. This idea is, of course, the foundation of many conclusions regarding the potency of endocrine products—"the test of results" referred to frequently.

The suggested daily dosage of liver extract is from three to six vials (each containing the equivalent of 100 Gm. of fresh liver). In pernicious anemia a maintenance dose, determined by the clinical response, is continued indefinitely.

Occasionally it may be inconvenient to give regular and prolonged doses of liver extract, and J. E. Connery, of New York (*Jour. Am. Med. Assn.*, Aug. 29, 1931, xcvii, p. 605), reports having given single massive doses of Liver Extract No. 343 with advantage. These doses ranged from thirty to fifty vials, equivalent to from 6 to 10 pounds of fresh liver!

The product known as Heparnucleate* is a combination of an active hemopoietic liver fraction, one part of which represents thirty-seven parts of fresh liver, with the nucleate of iron (originally, in 1927, sodium nucleate was used). Each vial contains 4.5 Gm. of the powder, 3.5 Gm. of which is the liver ingredient, equal to 125 Gm. of fresh liver, and 0.5 Gm. is the nucleates of iron and sodium. This is an average daily dose, although it is well to give double this amount daily for the first week. Anemia of every degree has been controlled by this new hemopoietic remedy.

PARENTERAL THERAPY—Usually little inconvenience results from giving liver extract over a long period. It does not taste so bad and only rarely causes discomfort. Occasionally, however, one finds those who are offended by it. Also, some pernicious anemia patients, after having done well on this treatment for several weeks or months, gradually fail to respond as previously.

In order to obviate these two difficulties, attempts have been made in various places to develop a hemopoietic liver extract for injection. For example, in Germany, M. Gänsslen, of Tübingen (*Klin. Wchnschr.*, Nov. 8, 1930, ix, p. 2099), reports his experience with a liver solution for intramuscular injection. An injection of one ampule of 2 cc., equal to 5 Gm. of fresh liver, has been claimed to cause a reticulocytosis as marked as that from 300 to 500 Gm. of fresh liver given by mouth.

Since then a preliminary publication by W. B. Castle and F. H. L. Taylor, of Harvard University (*Jour. Am. Med. Assn.*, April 11, 1931, xcvi, p.

1198), outlines a method of producing a solution of the original "fraction *G*" of Cohn, Minot, and their associates. Derivatives of this fraction were still further purified by washing with ether, and single intravenous injections containing approximately 0.1 Gm. per kilogram of body weight were administered. These Boston writers state:

"This solution was so prepared that 20 cc. contained the amount of material derived from 100 Gm. of liver; *i.e.*, about 4.5 Gm. of a commercial preparation of fraction *G*. After solution, a small insoluble residue was removed by careful filtration or centrifugating and the resulting clear dark reddish brown liquid sterilized by boiling for five minutes."

In view of the quite marked, though fleeting, depressor effect of the Boston solution, it must not be injected faster than at the rate of 2 cc. a minute. Despite this, the product has been found suitable for clinical use, and is highly potent. For example, in the summary of a later paper by M. B. Strauss, Castle, and Taylor (*Jour. Am. Med. Assn.*, Aug. 1, 1931, xcvii, p. 313), it is stated that

"Maximal reticulocyte responses were obtained from the daily intramuscular injection of the extract derived from 10 Gm. of liver."

This preparation apparently is not yet available, but in this country, Heparhemin,* in England, Hepatex V.P.T., and in Germany, Hepatopson *pro Injectione,* all represent deproteinized fractions of different hemopoietic potencies which are intended to be given by injection. In view of the possible depressor effects, the intramuscular injection is preferable.

It is my personal opinion that liver therapy per os should be continued as before in the majority of cases, leaving the injection method for the rarer cases referred to above and as a means of pushing the treatment in certain extreme circumstances.

LIVER EXTRACTS

Detoxicative

ANABOLIN* (1A)—A physiologically standardized alcoholic liver fraction containing the detoxicating hormone, each cubic centimeter of which contains 12 "units" (*i.e.*, it is capable of reducing the blood-pressure of a 10-kg. dog by 12 mm. Hg.). Used in hypertension, eclampsia, and many conditions of defective hepatic detoxication. Obtainable in two strengths: Anabolin Solution (12 units per cubic centimeter) and Anabolin Fortior (25 units per cc.) Dose: From 6 to 25 units intramuscularly each day, or as needed.

ANABOLIN TABLETS* (1A)—Each tablet contains the standardized active substance in 1 cc. of standard solution. Dose: From 1 to 3 tablets daily, in conjunction with injections (above), and to continue treatment.

EUTONON (1B)—An active principle extracted from liver by the method of G. Zuelzer. It is free from albumin, and is given by intramuscular injection in heart muscle diseases, angina pectoris, etc. (*Promonta, Hamburg.*)

HEPARMONE (1A)—An alcoholic fraction of liver containing the depressor principle. Used in hypertension, eclampsia, etc. Dose: 1 cc. or more each day by intramuscular injection. *(Eli Lilly and Co.)*

YAKRITON (1A)—A solution containing "the detoxicating hormone of the liver." Vials of 5 cc. each containing 5 Sato rabbit-ammonia-units. *(Sankyo Co., Ltd., Muromachi, Tokyo.)*

Hemopoietic

COPRON (1B)—Liver extract with iron and copper for use in pernicious and nutritional anemias. Each capsule represents approximately: fresh liver 10 Gm., iron 7 mg., and copper 0.27 mg. Dose: From 3 to 5 capsules t. i. d. *(Abbott Laboratories.)*

HEMOPOIETIN (2)—A technical name given to the alleged "hemopoietic hormone of the liver" which, when administered by mouth, exerts a marked reticulocytogenic influence in serious forms of anemia.

HEPANEME (1B)—Cachets of a concentrated extract from calves' liver with protoxalate of iron. Used in the treatment of anemia. Dose: From 6 to 18 cachets a day. *(Lab. de Biologie Appliquée, Paris.)*

HEPARHEMIN* (2)—A deproteinized solution of the alcoholic hemopoietic fraction from beef livers. Each cubic centimeter equal to 20 Gm. of fresh pulp. Hematinic. Dose: 5 cc. daily by intramuscular injection.

HEPARNUCLEATE* (1B)—A compound hematinic product consisting of a potent water-soluble liver extract and certain nucleates. (Sodium nucleate alone was used originally.) In vials of 4.5 Gm., each representing 3.5 Gm. hemopoietin (equal to 125 Gm. fresh liver) and 0.5 Gm. of ferric and sodium nucleates (iron 15 mg. and phosphorus 25 mg. per dose), with lactose q.s. Dose: The contents of one vial daily. It is best to double this dose during the first week of treatment.

HEPATEX—A soluble liver extract, each teaspoonful representing 2 oz. of fresh liver including the full vitamin-*B* complex. Used in anemia, debility, and as a general tonic. Dose: One or more teaspoonfuls *p.r.n. (Evans Sons, Lescher & Webb, Ltd., Liverpool.)*

HEPATEX P.A.F.—A sterile solution of the liver fraction suitable for intramuscular or intravenous injection. Used in cases of pernicious anemia in which an immediate response is essential. Ampules of 5 cc. Dose: The contents of one ampule daily. *(Evans Sons, Lescher & Webb, Ltd.)*

HEPATOPSON—A brown powder with a pleasant taste. Each gram equivalent to 5 Gm. of fresh liver. Used in pernicious and other serious anemias. Daily dose: 10 Gm. with a meal, mixed with the food. *(Promonta, Hamburg.)*

HEPATOPSON PRO INJECTIONE—A solution of the hemopoietic liver fraction for use in anemia. Each cubic centimeter equals 10 Gm. fresh calves' liver. Dose: 1 cc. or more by intramuscular injection. *(Promonta.)*

HEPATROL (1B)—A liquor concentrate of calves' liver in ampules for oral administration. Each ampule of 10 cc. equals 125 Gm. of fresh liver. Dose: From 1 to 3 ampules by mouth daily. *(Albert Rolland, Paris.)*

LIVER EXTRACT No. 343 (1B)—A water-soluble non-protein liver fraction. Each vial (containing from 3 to 4 Gm.) equals 100 Gm. fresh mammalian liver. Dose: The contents of from 3 to 6 vials daily. *(Eli Lilly and Co.)*

LIVER EXTRACT No. 55 (1B)—A modification of the foregoing to which iron ammonium citrate has been added (15 Gm. in each trade unit equal to 6½ lbs. of fresh liver). Dose: From 2 to 4 level teaspoonfuls a day. *(Eli Lilly and Co.)*

SOL. LIVER EXT. PARENTERAL—A sterile, aqueous solution of a concentrated water-soluble nitrogenous non-protein fraction from mammalian liver. Each ampule of 5 cc. contains the hemopoietin in 100 Gm. of fresh liver. For use in the treatment of pernicious anemia. Dose: One ampule daily by intramuscular or intravenous injection for three or four days; thereafter, one such injection a week. *(Lederle Laboratories, Inc.)*

14. THE MAMMÆ

Experimental Proof Lacking—Endocrine Control of the Mammæ—Mammary Functions—Clinical Use of Mammary Extracts—Mammary Products.

THE STATUS of research in this field of endocrine affairs is unfortunate. Physiologists have made the decision that the mammæ are not endocrine organs; so how can one get anywhere in an experimental way? The clinicians have concluded that, despite numerous encouraging reports, there are no prospects from mammary therapy; hence, why should we bother with it?

EXPERIMENTAL PROOF LACKING—In the book, "Glandular Therapy" (Chicago, American Medical Association, 1927, p. 98), W. A. Puckner says that, although mammary gland preparations were admitted to "New and Nonofficial Remedies" when there was promise of their value, they were omitted later because very slight evidence of their therapeutic value had accumulated during the years of their trial. In order to determine the present status of mammary products, letters were sent to a number of men supposed to be familiar with the subject. Says Puckner:

"The appeal was made to a leading gynecologist, a leading obstetrician, a leading pharmacologist, and a man closely identified with the field of internal secretions. Answers such as the following were received:

" 'To be very frank, I am quite unfamiliar with any benefits derived from the use of mammary gland preparations.'

" 'I do not know of one single piece of scientific work justifying the use of mammary gland preparations.'

" 'I beg to state that it is my opinion that there is available too little scientifically valid evidence on the problem to justify a report at this time.'

"These reports indicate that there is no clear-cut evidence to show that the administration of mammary gland preparations is of value; therefore the Council gave up the project of having an article on mammary gland preparations included in this series."

Then it must be admitted that the methods of experimental research are seriously limited, for the removal of the mammary tissue causes no especially notable changes—the mammæ are not vital endocrine organs like the parathyroids or the adrenals. Again, one can feed mammary substance to animals for weeks with no particularly interesting developments. Further, there are many far more fascinating byways in endocrine research.

For the benefit of the reader, and as a defense of the position I have taken for years, it is necessary to substitute reports of experimental research with clinical conclusions. After all, our interest in mammary therapy is only clinical, and so long as we can use this agent with advantage it should be immaterial whether the matter is ever reopened by the physiologists.

ENDOCRINE CONTROL OF THE MAMMÆ—First of all, it may be stated that the relationships of the mammary functions are suspiciously endocrine in character. The initiation of the growth of the breasts in conjunction with the development of the other secondary sex characteristics is dependent upon the ovarian hormone, which in turn is dependent upon the anterior pituitary sex hormone. Again, the so-called mammary hormone of Lane-Clayton and Starling (*Proc. Roy. Soc.*, 1905-1906, lxxvii, p. 505), believed by these workers to originate in the fetus, plays a part in the functional arousing of mammary activity and, later, lactation. The peculiar incidents noted in the Blazek pygopagous twins (70), where pregnancy in one caused a perfect cycle of mammary activity *in both,* demonstrates conclusively the humoral rather than the nervous character of these stimuli (*Deutsch. med. Wchnschr.*, 1910, xxxvi, p. 897).

Previous to this, A. Ribbert (*Arch. f. Entwcklngsmechn.*, 1898, vii, p. 4) had shown that mammary development was not under nervous control. He transplanted some mammary tissue from a virgin rabbit into a pregnant one, and the transplanted tissue grew and actually secreted milk.

MAMMARY FUNCTIONS—From the every-day clinical point of view, we know that the mammary tissue has other duties that fit in with the work of the other units of the reproductive mechanism to harmonize and correlate their functions. For example, there is abundant evidence to confirm the fact that during nursing there is a reflex action—at one time considered to be nervous in character but now believed to be hormonic—which furthers the involutionary changes in the uterus; and it is well known that women who do not nurse their infants, often suffer from subinvolution. This point has been confirmed by the evident advantage of mammary therapy in the treatment of subinvolution (96) as well as of agalactia (70).

The relation between mammary development and function and the ovaries is very intimate. Experimental evidence, which is amply confirmed by clinical experience, indicates that the ordinary corpus luteum that matures in connection with each menstruation exerts a normal hypertrophying effect on the mammary tissue. But the corpus luteum of pregnancy seems to have a still more marked and decisive influence on the utero-ovarian monthly service. It is the normal antiperiodic ovarian factor, which is discussed elsewhere (11).

Some recent experimental work with mammary extract confirms its effect on the uterine muscle. M. dal Collo Bonaretti, of the University of Naples (*Arch. di ostet. e ginec.*, Dec., 1922, xvi, p. 73), found that when she injected various mammary extracts made with Ringer's solution, a decided influence was exerted on the uterine muscle. This varied with the dosage. Small amounts

increased the tone of surviving uterine muscle and led to increased frequency and amplitude of the contraction. These results were the same in the gravid as in the empty uterus, and were produced by extracts of both secreting and inactive fresh tissue. Further, no specificity was demonstrable; that is, the uterus of one species responded to mammary extracts derived from another.

CLINICAL USE OF MAMMARY EXTRACTS—We now come to some of the clinical remarks that are on record in the literature. In his "Principles of Therapeutics" (Philadelphia, W. B. Saunders Company, 1921, p. 486), Oliver T. Osborne, of Yale University, makes this statement:

"The administration of mammary gland extracts will generally stop profuse menstruation, especially in young girls, and will also many times postpone to normal a too frequent menstrual cycle. . . . It is quite probable that the uterus involutes more rapidly and better when the woman suckles her child, possibly from the stimulation of the child at the breast, and as clinically demonstrated, the administration of mammary extracts will generally, if the cause is not pathologic, stop profuse menstruation.

"The only use for extracts of the mammary gland is in the profuse menstruation of young girls and young women, and in menorrhagia occurring at the time of the menopause; in other words, in functional bleeding."

W. A. Briggs, of Sacramento, California (*Endocrinology,* April, 1917, i, p. 191), discussing uterine hyperemia that occurs at the menopause and that also accompanies fibromyomata, remarks:

"Fortunately in the mammary gland, we have a powerful physiologic remedy which either antagonizes or neutralizes the ovarian hormone or inhibits its production or possibly acts more directly on the uterine circulation and nutrition. Whatever its mode of action, it seems to be by far our most effective remedy in controlling or regulating excessive or perverted ovarian function as shown by menorrhagia in its various forms."

In a discussion of Briggs' article, Samuel W. Bandler, of New York (*ibid.,* p. 198), remarks:

"Especially where perverted ovarian function is a responsible factor [in cases with uterine hyperemia and fibroids] mammary extract seems to be the natural drug for prophylactic purposes. Mammary extract controls the bleeding from the uterus in many cases, since its relation to the ovary is undoubted. . . . The writer has conservatively treated a large number of cases associated with menorrhagia and metrorrhagia by the use of mammary extract, ergot, and hydrastis, and in some cases by the use of irradiation of the ovaries. The results are certainly most excellent and have in a great measure done away with a surgical treatment of these cases."

Numerous European reports confirm these findings. For example, Hoehne, who writes from Stoeckel's clinic at Kiel, has worked out this treatment on a thoroughly scientific basis. He shows that it is beneficial in diminishing an

excessive menstrual flow as well as in controlling its unusual duration. As it is useful in lengthening abnormally short intervals between the periods, it tends to restore a more nearly normal menstrual rhythm in women in whom an excessive and too frequent flow has been the rule.

G. Pochon, of Paris (*Jour. de méd. de Paris,* 1909, xxi, p. 195), states that both clinically and experimentally "the mammary hormone" has a tendency to facilitate uterine depletion. Another French author, J. Battuaud (*Rev. d. mal. de la nutr.,* 1909, vii, p. 260), advises this form of medication, especially in flooding in young girls and in climacteric menorrhagia.

Henri Vignes, of Paris, in his comprehensive book, "Physiologie gynécologique et médecine des femmes" (Paris, Masson & Cie, 1929), makes a number of references to mammary therapy. For example (page 514):

"Some authors suggest that an internal mammary secretion may exist, and it is chiefly upon the results of mammary therapy that this hypothesis is based.

"Organotherapy with mammary gland extracts has been used by a good number of physicians since the year 1894. Some of them have no faith at all in its efficacy, while others praise it loudly; for example, Battuaud, one of the first in France to have recourse to it, said: 'In a general way it may be stated that mammary organotherapy is indicated whenever there is premature occurrence of menstruation, a flow that is too profuse or too prolonged, or intercalary uterine hemorrhage, *a fortiori* when several of these pathologic conditions are combined in the same patient. . . . In about one-twentieth of the cases, mammary organotherapy is entirely inactive but in the other nineteen-twentieths its effects are considerable and sometimes rapid."

In another place (*ibid.,* p. 283) Vignes suggests that

"It is just possible that certain medicaments prevent the premenstrual *édification* [hypertrophy] of the uterine mucosa and that, accordingly, they may prevent profuse menstruation. I have several times wondered whether mammary extract acts in this manner."

It may be stated in conclusion that mammary organotherapy deserves a place in the armamentarium of every general practitioner, for it serves well in two distinct ways: as a galactagogue (70) and uterine involutant (96), and as an antiovarian measure in the control of menorrhagia (80).

MAMMARY PRODUCTS

MAMMARY EXTRACT (1B)—A desiccation of the glandular tissue from the udders of cows and ewes, each part representing eight parts of fresh tissue. Dose: From 5 to 15 gr. t.i.d. at meals.

MAMMIN (3)—A postulated active principle from lactating mammary tissue akin to galactagogin from the placenta *(q.v.)*.

MAMOS (1B)—A mammary extract in tabloid form each containing the equivalent of 5 gr. of the fresh tissue. Used in uterine hemorrhage or subinvolution and as a galactagogue. Dose: From 1 to 3 tablets t.i.d. *(Burroughs Wellcome & Co.)*

15. THE PANCREAS

Autonomin—Angioxyl, Kallikrein, Padutin—Panocrin—Insulin, Iletin —Pan-Secretin*—Pancreatin—Pancreas Products.*

THE DISCOVERY of insulin, or rather its triumphal perfection in 1922, did more to establish faith in organotherapy than any previous event; since then, the remarkable accomplishments with liver therapy have increased this faith still more. It is surprising, however, how many more possibilities there are in pancreas therapy than the known and appreciated value of insulin in diabetes. It seems that the pancreas is destined to be the source of at least three valuable remedies—and possibly more.

AUTONOMIN—For a number of years research workers have sensed an antagonism between certain endocrine glands, and it is well known that there is a balance between the pancreas and the adrenals. Much of this influence has to do with the sympathetic system, hence the reader's attention is called to the suggestions of H. Eppinger and L. Hess, of Vienna, in connection with their studies on sympathicotonia and vagotonia (91). In the course of their research, these workers postulated a hypothetical sympathetic regulator to which they gave the name "autonomin." It was believed to originate in the pancreas and to serve continuously as a hormonic governor of the endocrine systemic balance.

In the years that have passed, autonomin as such has eluded isolation; but, as will be seen shortly, several other important advances have been built upon the foundation-stones laid by these Vienna workers.

ANGIOXYL, KALLIKREIN, PADUTIN—Within the last three years, the profession has discovered that there are physiologically active extracts of the pancreas that do not have any noteworthy effect on carbohydrate metabolism. Based on research work done in the Collège de France in Paris and at the University of Berlin, there have been developed two similar pancreatic extracts known as the "circulatory hormone of the pancreas." A long and comprehensive review of the French phase of the subject appears in *La presse médicale* (Oct. 2, 1929, xxxvii, p. 1279), in which N. Kisthinios and his associates recount the preliminary researches and outline the clinical possibilities of this new product.

The seed from which this new development has come was the accidental noticing of beneficial cardiomuscular reactions in certain patients receiving insulin. Particularly was this true in connection with the treatment of diabetic patients suffering from anginal attacks. The idea then suggested

itself to try insulin in patients with angina but not diabetes, and these French workers were surprised to find that in several instances there was an almost immediate cessation of the crises. It was concluded that the beneficial cardiomuscular reactions were not due to the sugar-reducing influence of insulin but to another substance associated with insulin in greater or less amounts. At first, this was considered to be an impurity, and pains were taken to prove that it had nothing to do with the peptones, choline, or histamine—substances frequently found in organotherapeutic products and which may mask the clinical response.

Pierre Gley and N. Kisthinios, with their associates, finally isolated this substance and demonstrated that, although it has no ability to reduce sugar, it is capable of bringing about marked circulatory changes, including a reduction of the blood-pressure.

The separation from insulin of the circulatory hormone, Angioxyl, is not a simple matter. While it has been used quite extensively and the reports indicate that it has real potentialities (45), the product will probably be improved materially. When this is done, exactly the same thing will have happened as with insulin, for the original product is hardly comparable with the preparation now in general use.

Parallel with these French investigators, German workers under the direction of E. K. Frey were carrying on researches with the circulatory hormone (*München. med. Wchnschr.*, Nov. 22, 1929, lxxvi, p. 1951). Their experiments originated along somewhat different lines. They succeeded in isolating from the urine a substance with a marked vasodilator effect. On further investigation, this was traced to the pancreas and its origin verified, for after pancreatectomy the amount of this substance in the urine was found to decrease markedly.

As a result, the German reports claim that this new hormone exists in an active as well as an inactive form in the body. While it is found in active form in various tissues and in the blood, it is also present in an inactive form linked, so these workers believe, to another polypeptide substance. Frey suggests that this related product bids fair to be one of the most potent of the organic extracts, for so little as one five-millionth of a gram of this polypeptide inactivator is capable of counteracting the effect of a known amount of the circulatory hormone.

The subject is complex and still in the early stages of its development, but it is interesting to know that the relation between the circulatory hormone and this inactivating principle has been found to depend upon the prevailing reaction of the tissues. With the slight shifting toward the acid side brought

about by an accumulation of acid metabolic products, there is released a portion of the inactive link between the hormone and the inactivator whereby the vasodilator action comes into operation. In this alternation between the union of these substances and their releasing, which is brought about by slight changes in hydrogen-ion concentration of the body, Frey detects the real physiological importance.

This circulatory hormone has received the strange name "Kallikrein,"† and has been used with some encouraging clinical results as a means of dilating the blood-vessels, especially in hypertension and angina pectoris. More recently another name for it, Padutin, has crept into the literature.

E. Leschke, the Berlin internist (*München. med. Wchnschr.*, Ser. 5 1930, lxxvii, p. 1524), recommends Kallikrein in "vegetative nervous, thyrotoxic, and essential hypertonia, in angioneurosis, and vascular disorders with trophic disturbances, angina pectoris, cerebral angiospasm, and in varicose ulcers and gastric and duodenal ulcers." The circulation hormone of the pancreas is an antagonist to epinephrine and increases the excitability of the parasympathetic system. The good effect of Kallikrein on alimentary ulceration is explained by an improvement in the perfusion and nutrition at the base of the ulcer, a condition analogous to that observed by Frey who also claims "improved formation of callus and more rapid healing of bone fractures," under this circulatory regulative influence.

PANOCRIN*—An insulin-free pancreas product, which is essentially circulatory in its effects, is known in this country as Panocrin.* Apparently it is a true internal secretion which enters the blood stream and circulates through the organism, bringing about by catalytic action, changes that regulate the physiological chemistry—"the pancreas circulatory hormone." The counterpart of this substance is excreted by the kidneys and appears in the urine, where its presence can be demonstrated. After its experimental injection, the mobility of the pulse is increased, but simultaneously the blood-pressure begins to fall. Panocrin can be assayed biologically by its ability to lower the blood-pressure, and it must be added that histamine, which is also a depressor substance, is not present in physiologically active amounts. There is some similarity between insulin and Panocrin in their influence on unusually high pressure values, but blood-pressures within the normal range are not affected by this principle.

Attention has been drawn elsewhere (12) to the so-called "heart hormone," but it should be stated here that Panocrin does not contain any

†On reading the proof of this chapter, a friend advises that *kallikreas* was the name given to the pancreas in the time of Hippocrates.

substance with such an influence, but is rather a "circulation hormone" that exerts a controlling effect on the blood-pressure through its regulation of the circulation. Panocrin is used chiefly in angina pectoris, and early reports indicate that it gives symptomatic benefit. No cases have been cured, nor can it be claimed that its blood-pressure-regulating effect offers a better weapon than Anabolin (13) in the toxic, functional cases. Panocrin may find a wide range of usefulness because it reduces muscular spasm like that found in various simple and serious conditions—from the menopause on one hand, to gangrene on the other. Strangely enough this method has been used in certain cases of low blood-pressure with an increase in the figures, thus confirming the German impression that this agent is a regulator of body chemistry rather than a pharmacodynamic remedy.

Developments along this line already have demonstrated once more that, despite the spectacular accomplishments in organotherapy, there are still many wonderful things "just around the corner."

INSULIN, ILETIN—As far back as 1910, Sir E. S. Schafer, physiologist in Edinburgh University, called the Langerhansian hormone, or pancreatic internal secretion, "insulin." It was known and quite well understood for many years before its isolation in 1921.

The history of this epoch-making development, which brought the Nobel prize to F. G. Banting and C. H. Best, of the University of Toronto, as a reward for an outstanding accomplishment in medical science, is worth recalling if only to show how near to success many a worker can come and yet fail, and how easy a trick it was in the end. I shall quote first from an excellent editorial review in the *Medical Woman's Journal* (June, 1924, xxxi, p. 176):

"A brief survey of the difficulties encountered in the preparation of suitable pancreatic extracts may be of interest. These difficulties may be classed under four headings: (1) the destruction of the active principle by oral administration; (2) the toxicity of the first types of extracts when given intravenously; (3) the interference of the enzymes contained in the acini when extracts were made of the whole gland; and (4) the influence of the medium used for extraction.

"Rennie and Fraser (1907) tried the oral administration of an extract made from the Langerhansian islets of certain bony fishes, but they found that the symptoms of diabetes were not affected by this method of treatment. Zuelzer (1908) all but succeeded in obtaining a suitable extract, which he administered intravenously and which resembled Insulin in many respects; but the reactions, fever and nausea, which his extract produced, kept him from following up his partial success. Crofton (1910) found that the ferment of the acini (trypsin), which destroyed the active principle of the islets,

could be eliminated by heating pigs' pancreas to 80° C., and that the process of heating left the products of the islets unchanged. E. C. Scott (1911) ligated the pancreatic ducts in order to produce a degeneration of the acini, which would eliminate the external enzymes; but he failed to block the ducts completely, so that his extract was not free from the products of the acini, and as he used 95 per cent. alcohol for extraction, in which the product of the islets is but slightly soluble, the active principle was present in very small amounts in the preparations which he used; but this method of procedure was turned to account by Banting and Best. Murlin and Kramer (1912) obtained a temporary storage of glycogen by the use of acid extracts. Unfortunately the acid preparations were alkalinized before injection and thus rendered useless, for, as Murlin says, 'The antidiabetic substance was destroyed, or at least obscured by using too much alkali.' The results obtained by Banting and Best (1921) were secured by means of extracts made with 60 per cent. alcohol which had been acidified by addition of 0.2 per cent. hydrochloric acid. The first preparations were made from the pancreas of a dog, in which complete degeneration of the acini had been produced by complete occlusion of the ducts; subsequently fetal calf pancreas, in which the islet tissue predominates, was used; finally extracts from beef pancreas were made, which not only eliminated the symptoms of diabetes in depancreatized animals, but also proved effective when administered to diabetic patients. The use of 95 per cent. alcohol proved to be of value for the precipitation of the active principle from the initial extracts. Various methods, described by Best and Scott (1923), were employed in the course of time to perfect the method of extraction, to purify the final product, and to insure the maximum yield of Insulin. The largest yield obtained so far has been 900 units of purified Insulin from fifteen pounds of beef pancreas. Collip contributed towards the purification of the final process."

Some more history can properly be recorded here, for it is an education in endocrinology to follow the events that led up to this great accomplishment. Banting himself told the intimate story in the Cameron Lecture delivered before the University of Edinburgh in 1928 (*Edinburgh Med. Jour.*, Jan., 1929, xxxvi, p. 1).

It was in November, 1920, that Banting conceived the original idea after reading an article by Moses Barron, of Minneapolis (*Surg. Gynec. and Obst.*, Nov., 1920, xxxi, p. 437), in which attention was called to an analogy between the degenerative changes that follow the experimental ligation of the pancreatic duct and the blockage of the duct by gall-stones. This idea grew on Banting until he got up in the night and made this entry in his note-book: "Ligate pancreatic ducts of dogs. Wait from six to eight weeks for degeneration. Remove the residue and extract." Then followed the trip to Toronto and the discussion with J. J. R. Macleod, of the Department of Physiology in the University there, and the request for permission to carry on these experiments.

Work began in May, 1921, and C. H. Best, then a medical student, was the chief chemical assistant. The first attempts were failures, but on July 27 pancreatic degeneration was produced and the saline extract of the degenerated gland was made and injected into a depancreatized dog. The blood sugar fell from 0.2 to 0.11 in two hours, with marked clinical improvement. Another depancreatized dog was kept in good condition for eight days by using an extract from five degenerated pancreases. This exhausted the available supply, and the dog rapidly became moribund. It was then suggested that the pancreas might be exhausted by continued injections of secretin, extracting the exhausted pancreas thereafter. This was done, and the extract restored the moribund dog to a fairly normal condition. This emphasized the principal theory that the active principle was an extract of the island cells, free from the products of the acinous cells.

Then followed attempts to obtain such extracts more conveniently. Fetal calves' glands were tried, since they are rich in islet tissue. Experiment showed that fetal pancreas extracts lowered the blood sugar of depancreatized dogs, and thus an assertedly cheaper and more plentiful source of isletin was discovered. This active principle could be extracted from the fetal glands with acetone and alcohol, and it was not destroyed by chloroform or ether. Alcoholic extracts of full-grown pancreases were next made, and with various extracts a depancreatized dog was kept alive for seventy days.

On January 11, 1922, the first diabetic patients were treated with the pancreatic extract in the Toronto General Hospital. Sterile abscesses were caused because of the unusually high percentage of protein, but the clinical improvement was sufficient to cause a large proportion of the laboratory staff to attack the problem of producing a potent but harmless extract. J. B. Collip then developed a method of fractional precipitation by alcohol, which eventually produced a much less toxic and more potent product. While "isletin" was the name first used by these workers, Macleod insisted that it should be "insulin." It was found later that this name had been used about ten years before.

The problem of standardization was then attacked. An attempt was made to find a test-tube reaction of the potency, but none was found. It was necessary therefore to develop a biological method. Since Collip had found that the normal rabbit receiving a certain amount of insulin in four hours developed intermittent convulsions and coma, it was decided to use the rabbit in making the biological assay. As these laboratory animals recovered rapidly when given injections of glucose, they could be given other tests. A "unit" of insulin eventually was defined as the amount required to reduce

the blood-sugar index of a normal rabbit weighing 2.5 kg. to 0.045 in four hours. Later, to insure uniformity of strength in various countries, the Public Health Committee of the League of Nations changed the definition as follows:

"The unit of insulin is one-third of the amount of material required to lower the blood sugar of a 2-kilogram rabbit which has fasted twenty-four hours, from the normal level (0.118 per cent.) to 0.045 per cent. over a period of five hours."

As has been seen above, these clinical accomplishments were the outcome of many years of patient effort by numerous workers, for, as Banting himself puts it, "insulin was but the final stage."

The story of insulin has been told many times, and many hundreds of research workers have been heartened by this success. As a matter of fact, the present methods of fractional extraction—separating different substances by the use of various solvents—are the basis of a large number of successes along these lines, that have followed the advent of insulin.

PAN-SECRETIN*—After so stirring a story, it may seem out of place to tell my own experience, but it should be given. At the International Congress of Medicine in London in 1913, I was fortunate in meeting a number of students of endocrinology who at the time happened to be especially interested in diabetes. I had chats with Sir E. S. Schafer of Edinburgh, P. J. Cammidge of London, Heinrich Strauss of Berlin, W. M. Crofton of Dublin, and E. Gley of Paris. Professor Strauss invited me to Berlin, telling me of the work that was being done there by Georg Zuelzer. Professor Gley invited me to Paris, and Professor von Noorden to Frankfort. Numerous visits were made to all these places. It was from Crofton and Zuelzer that I got the first idea: In order to obtain the useful pancreatic endocrine product, one must interfere with the lytic changes brought about by the acinous digestive secretion. Zuelzer accomplished this as far back as 1908. Although his alcoholic pancreatic extracts were definitely potent in controlling hyperglycemia, they were not stable; and, compared with present preparations, were obviously crude. He was the first to discover the fact, rediscovered by Collip, that alcohol interferes with these digestive influences and thus can be made to protect the internal secretion.

Based on the personal suggestions of Crofton, the attempt was made to separate mechanically the acinous from the endocrine tissue. From that day to this, there has been perfected and in extended use, an extract of pancreas tails which, while actually containing no insulin, embodies an insulin-catalyst that is capable of furthering pancreatic function under certain circumstances (52). This product was combined with an extract of the duodenal cells

containing secretin (10) on the presumption that pancreatic insufficiency in diabetes was both a digestive and an endocrine defect, and that attempts should be made to reestablish both functions simultaneously. Later, the pancreas-tail-secretin combination was made available as Pan-Secretin Co.*

As the reader will see (52), this product is used as a means of reestablishing pancreatic activity. It has no immediate insulin effect, hence it cannot be standardized in the same way as insulin. Nevertheless, from a pharmaceutical point of view it is no different from a number of other endocrine products that are still in general use, including desiccations of the thyroid, adrenals, etc.

It is important to differentiate between substitutive insulin therapy, which introduces the pancreatic hormone obtained from other sources and thereby replaces the insulin that the patient himself is not able to produce, and the homostimulative pancreas therapy, which makes it possible for the pancreas to produce its own insulin. A careful distinction between these two methods will explain why the early attempts at pancreas therapy failed.

For clinical benefit to come from this treatment, it is necessary for the pancreas of the diabetic patient to accomplish a certain degree of its proper function and to possess the ability to react to the stimulation produced by the ingestion of the pancreas-secretin combination. This ability to react is the first condition for success in this therapy; another is that the treatment be continued for a sufficient length of time. This explains a number of the clinical experiences recounted elsewhere, particularly the failure of this treatment in juvenile diabetes, where apparently the disease is due to apancreatism, or pancreatic atrophy.

There is much more that might be said here, but some additional clinical data and some very interesting history will be found in Chapter 52.

PANCREATIN—So many new things are being spread before us that we are liable to forget the old. Pancreatin is an old therapeutic standby which is just as valuable as ever. In fact, by applying the fractional method of purification mentioned repeatedly in these pages, it has been possible to prepare more potent products than before.

Pancreatin is the digestive remedy made from the acinous tissue of the pancreas. It contains at least three active digestive ferments which, because of their physiological peculiarities, are named: trypsin, a protein-splitting ferment; amylopsin, a starch-splitting ferment; and steapsin, a fat-splitting ferment. All three of these ferments are present in the normal pancreatic juice. By administering properly prepared and standardized extracts, it is possible to enhance materially the digestion of all three of these types of food in the intestine.

Much has been written on the pancreatic ferments, but there is space here only to say that pancreatin is a nutrition-stimulating digestant capable of rendering a material service in almost all forms of malnutrition, indigestion, and alimentary toxemia.

PANCREAS PRODUCTS

ANGIOXYL (1B)—A fractional extract obtained from the pancreas, free from insulin and histamine. Believed to exert a specific trophic effect on blood-vessels. Used as a cardiac stimulant in angina pectoris and arteritis, and in hypertension with cardiac involvement. Obtainable in solution for intramuscular injection and in *sirop.* Dose: 1 cc. or more *p. r. n. (J. B. Fialip, Paris.)*

HOLADIN (1B)—A total pancreas extract in powder for oral administration. Used in chronic pancreatic insufficiency, alimentary indigestion, and diabetes mellitus. Dose: From 2 to 4 or more 5-gr. capsules after meals. *(Fairchild Bros. and Foster.)*

ILETIN (1A)—Insulin, Lilly. The first trade preparation of insulin *(q.v.). (Eli Lilly and Co.)*

INSULIN (1A)—An aqueous solution of the carbohydrate-regulating hormone of the pancreas islets, physiologically standardized to match the potency of the British Medical Council's standard dry insulin hydrochloride, 1 unit being equal to 0.125 mg. Used in diabetes mellitus and other nutritional disorders as a means of increasing the metabolism of carbohydrates. Obtainable in vials of solutions of varying strengths, from 10 units in 5 cc. to 100 units in 10 cc. Manufactured in numerous laboratories under license from the Governors of the University of Toronto. (U.S. Brands: *Lilly, Mulford, Squibb, and Stearns.)*

ISLETIN (1A)—The name originally given in Toronto to the pancreas (Langerhansian) hormone.

KALLIKREIN (Padutin)—A solution containing the circulatory hormone, or *Kreislaufhormon,* discovered by E. K. Frey and H. Kraut. It is found in the pancreas, and contains a thermolabile albumin body of high molecular content. Used in angina pectoris, arterial spasm, Raynaud's disease, and cardiovascular sclerosis. Each 1-cc. ampule contains 2 "biological units." Dose: 1 or more injections daily *p.r.n. (Bayer, Meister-Lucius, Leverkusen a. Rh.)*

PANCREPATINE (1B)—A combination of a "special extract" of pancreas and hepatic extract in gluteinized globules each containing 0.25 Gm. Used in diabetes mellitus. Dose: From 6 to 12 globules daily at meals. *(Laboratoires Laleuf, Paris.)*

PANKREON (1B)—A total pancreas extract combined with tannin, used as a pancreatic digestant. Dose: From 5 to 10 gr. after meals. *(Bayer, Meister-Lucius.)*

PANOCRIN* (1A)—A solution containing the circulatory hormone of the pancreas freed by fractionization from insulin and histamine. Used in certain circulatory disorders as angina pectoris, coronary sclerosis, organic hypertension, etc. Capable of physiological standardization. Dose: 1 cc. intramuscularly one or more times a day.

PAN-SECRETIN* (1B)—A combination of an active concentrate from the tail of the pancreas (Langerhansian islet tissue) and an acid duodenal extract containing secretin, seven parts of the former to three of the latter. Used to assist in reestablishing the two chief pancreatic services in diabetes mellitus (functional). Contains no insulin. Tablets of 5 gr. Dose: 3 or more q.i.d. The clinical findings are a guide to variations in dosage.

PANSULIN (1)—An insulin-containing extract for oral administration, the potency of which is claimed to have been physiologically standardized by H. Fornet. *(Inst. für Microbiologie, Saarbrucken.)*

TRYPSOGEN (1B)—A "homostimulative extract of the pancreas" (total) with 1/200 gr. each of gold and arsenic bromides. In tablets of 5 gr. Used in diabetes mellitus. Dose: From 2 to 5 or more tablets after each meal. *(G. W. Carnrick Co.)*

16. THE PARATHYROIDS

The Parathyroid Functions—Parathyrin—Paroidin—Para-thor-mone—Antiphymin—Standardization—Parathyroid by Mouth—Parathyroid Active Principles.

THE PARATHYROIDS are small, kidney-shaped bodies, usually four in number, situated on the posterior borders of the lateral lobes of the thyroid. The disastrous results that used to follow thyroidectomy a number of years ago are now known to have been due to removing the parathyroids as well, for, although these glands are related to the thyroid anatomically, they are independent of it functionally.

The two external parathyroids were discovered and described in 1880 by the Swedish anatomist, Ivar Sandström, while the anatomical and physiological independence of the parathyroids was proved in 1895 by A. Kohn, of Germany, who called them "the epithelial bodies."

Grain for grain, the parathyroid glands appear to be the most potent of all the endocrines. The parathyroids and the adrenals alone, among the exclusively endocrine organs, are absolutely essential to life.

THE PARATHYROID FUNCTIONS—It is evident that the parathyroids produce a hormone or chemical principle, carried through humoral channels, which is responsible for initiating certain of the metabolic activities. In 1907 C. Parhon and C. S. Urechie, of Bucharest, Roumania (*Neurol. Centralbl.*, 1907, xxvi, p. 1099), and in 1908 W. G. MacCallum and C. Voegtlin, of Johns Hopkins Hospital (*Johns Hopkins Hosp. Bull.*, 1908, xix, p. 91), observed the decisively beneficial effect of calcium in parathyroid tetany. Consequent upon this, MacCallum suggested that calcium metabolism is controlled by the parathyroids. From that time on, most of the students of parathyroid physiology made calcium studies in addition to observations of the nervous reactions.

In addition to the pioneer work of these men, W. F. Koch of Detroit (1913), D. Noël Paton of Glasgow (1916), H. W. C. Vines of Cambridge (1920), and others have shown that these little glands evidently are concerned with the destruction of certain waste products in the nature of protein-split products, like guanidine, that are unusually potent and seem to have a predilection for affecting the nervous system. Their hormone also makes it possible for the body to retain calcium in suitable form, probably in the colloidal state. A mass of experiments has shown calcium to be most important in regulating the body's reactivity to various external impressions, especially infections, and the parathyroid hormone is often called a "calcium mordant."

Soon after MacCallum, Koch, and others had demonstrated the influence of the parathyroids on calcium metabolism, W. R. Grove and H. W. C. Vines, of Cambridge (*Brit. Med. Jour.*, Oct. 29, 1921, ii, p. 687), began their study of the relation of ulcerative conditions to calcium metabolism. Early in 1921 Vines (*Jour. Physiol.*, May, 1921, lv, p. 86) submitted evidence showing that in the circulating blood of normal persons calcium is present in ionized and combined forms and that, when coagulation occurs, the calcium in exuded serum is in ionized form, the normal amount present being about 10.5 mg. of calcium per 100 cc. of blood. Grove and Vines found that in certain ulcerative conditions there was a deviation from the normal, some of the calcium being present in the combined form. This was true in all cases of varicose ulcer. In order to increase the ionic fraction of the calcium in the serum, they administered intramuscular injections of ionized calcium, which helped to promote the commencement of healing in the ulcer; oral administration was effective. These authors remark (*Brit. Med. Jour.*, May 20, 1922, i, p. 791):

"But the injections did not appear to have the power to cause complete healing, and it was not till parathyroid substance was given orally that complete healing was obtained. Further, it was observed that healing of the ulcer and rise in the ionic calcium content of the serum ran approximately parallel. From these observations it was concluded that the toxic substance produced by the varicose condition in some way injured the parathyroid glands, and also combined with some of the ionized calcium of the blood. In this way, the calcium balance of the blood became disturbed, and the parathyroids were not able to rectify it. Finally, the decrease in the plasma of one of its normal constituents would tend to lower the resistance of the tissues, so that the ulceration, started by slight local trauma, would tend to occur within the varicose area, where nutrition of the tissues is least."

PARATHYRIN—So far as is known at present, there is only one parathyroid hormone, sometimes called parathyrin, and it has two dissimilar but related duties. Perhaps some day this substance will be divided as have several other endocrine principles, and we shall find that each part is responsible for one of these two duties: (1) The regulation of the calcium metabolism, and (2) the destruction of the protein-split products in the nature of guanidine and methylguanidine.

For more than a quarter of a century before the hormone of the parathyroid glands was prepared in a concentrated, potent form, investigators were working with crude extracts in an attempt to relieve the symptoms of thyroparathyroidectomy. The first reports of success are ascribed to G. Moussu, a French physician who in 1898 (*Compt. rend. Soc. de biol.*, 1898, p. 867) described his experiments in which tetany was relieved by

subcutaneous and intravenous injections of water or glycerin extracts of horse parathyroids. In 1905 G. Vassale, of Turin (*Arch. ital. d. biol.*, 1905, xliii, p. 177; *ibid.*, xx, p. 149), reported the successful treatment of eclampsia and infantile tetany with his extract, *paratiroidina,* but he failed to describe his method of preparing it. Evidently it was just a concentrate.

In the following year W. G. MacCallum (*Brit. Med. Jour.*, 1906, ii p. 1282) stated that benefit was derived in infantile tetany if emulsions of parathyroids were given by intraperitoneal injection. The nucleoprotein extract of S. P. Beebe, of New York (*Am. Jour. Physiol.*, 1907, xix, p. 13), was used with success by several independent workers in the treatment of tetany, and two years later W. N. Berkeley and S. P. Beebe (*Jour. Med. Res.*, 1909, xx, p. 149) described their method of extracting this nucleoprotein with a slightly alkaline saline solution. It was found, however, that their extracts were very unstable, which led them to believe that the active substance was really an enzyme. This, however, was an error, as will be seen.

W. G. MacCallum and K. M. Vogel (*Jour. Exper. Med.*, 1913, xviii, p. 618) prepared an extract from bovine parathyroid glands with Ringer's solution and glycerin. Intravenous injections of this extract into thyroparathyroidectomized dogs allayed the tetany temporarily without detectably affecting the blood calcium. To them, this suggested that there is in the parathyroid some substance that alleviates tetany but has no effect on serum calcium, although it apparently influences the central nervous system. Probably their product was too crude or not sufficiently potent.

PAROIDIN—For the next decade little additional knowledge was published regarding the production of effective parathyroid extracts. Then Adolph M. Hanson, of Faribault, Minnesota (*Mil. Surgeon,* March, 1923, lii, p. 280), announced the perfection of an extract prepared with dilute hydrochloric acid, which he called the "hydrochloric-X." In the same journal for January, 1924 (liv, p. 76), he described his method of preparing the hydrochloric-X as follows:

"Fresh bovine parathyroid glands (freed from fat as much as possible, without removing parts of the glands) finely divided	30 Gm.
Pure distilled water	495 cc.
Concentrated hydrochloric acid (C.P.)	5 cc.

"This is boiled for two hours, the solution allowed to cool, and made up to 500 cc. with pure distilled water. Most of the fat is removed by the ordinary process of skimming, some adheres to the container. It is then filtered through sterile gauze and, finally, through sterile fine mesh filter-paper."

This extract relieved tetany in parathyroidectomized dogs (*Minnesota Med.,* May, 1925, viii, p. 283) and was capable of increasing the serum calcium of thyroparathyroidectomized dogs on a meat diet, with complete prevention of tetany. This was the first dependable extract, the potency of which was determined in the laboratory. It was made available as Paroidin, in 1928. Standardization methods will be discussed shortly.

Hanson attempted further purification with phosphotungstic and picric acids, obtaining active extracts. The phosphotungstic acid precipitate was insoluble in any of the ordinary solvents, and because of this could be tested only when given orally.

In May, 1924, Louis Berman, of New York (*Proc. Soc. Exper. Biol. and Med.,* May, 1924, xxi, p. 465), outlined his results with an acid alcohol extract of ox parathyroids. Blood calcium was increased and tetany relieved after administration of this extract.

It is undoubted that the extracts of many of the early investigators contained some of the parathyroid hormone, and unquestionably Hanson had developed an extract of measured activity when, in 1925, J. B. Collip, then of the University of Alberta, published the preliminary papers in his series of detailed studies of the parathyroid hormone (*Jour. Biol. Chem.,* March, 1925, lxiii, pp. 395, 439). His extract was prepared from beef parathyroids by heating for one hour with 5 per cent. hydrochloric acid. The solution was made slightly alkaline, and the proteins precipitated with hydrochloric acid. This precipitate included the active substance by means of which Collip could control or prevent tetany in parathyroidectomized dogs. His protocols cover experiments with thirty-five dogs treated with the extract either orally, subcutaneously or intravenously. Oral administration relieved tetany without causing much change in the blood calcium. Subcutaneous administration was most effective (*Jour. Biol. Chem.,* June, 1925, lxiv, p. 485).

Heavy doses of the extract can produce in normal dogs symptoms of hypercalcemia, the degree of which is directly proportionate to the amount of the hormone given. In either normal or parathyroidectomized dogs, overdosage causes a definite chain of symptoms including anorexia, vomiting, weakness, and collapse, and ending in death if terminal symptoms are allowed to develop.

PARA-THOR-MONE—In view of the experience with insulin, which was perfected in, and patented by, the University of Toronto (15), the University of Alberta made a somewhat similar arrangement for the manufacture of the Collip extract, known as Para-thor-mone. The aggressive

emphasis of this product seems to have lessened the credit due the earlier workers in this field, especially A. M. Hanson.

Collip's preferred method of preparation is as follows: The ground glands are heated at 100° C. with 5 per cent. hydrochloric acid for from thirty to sixty minutes. To this is added four parts of water. The fat is removed, and the pH changed to 8 or 9. An isoelectric precipitation is carried on to remove inert substances by adding hydrochloric acid to pH 5.5. The filtrate from this precipitation is saturated with sodium chloride. The active substance precipitates, and is purified by repeated isoelectric precipitations. For injection, it is dissolved in hydrochloric acid at pH 3.0 and passed through the Berkefeld filter. Further purification may be carried on by solution of the active principle in alcohol, followed by precipitation with acetone and ether.

From a survey of the literature immediately following Collip's announcement of his extract, it appears that at least a half dozen other laboratories were using effective parathyroid extracts at the same time. Among these was Hans Schulten, of Hamburg (*Klin. Wchnschr.*, Dec., 1925, iv, p. 2487), who extracted horse parathyroids with N/10 hydrochloric acid. In normal dogs he obtained a rise in serum calcium, which was at its maximum thirty-six hours after a single injection.

Again A. M. Hjort and associates in Detroit (*Jour. Biol. Chem.*, Aug., 1925, lxv, p. 117) presented protocols showing that either aqueous or alcoholic extracts of bovine glands were active. The hormone is relatively stable, since boiling for two hours does not harm it, and, further, Hanson's original hydrochloric-X showed no loss of activity after sixteen months on ice.

N. F. Fisher and E. Larson, of the University of Illinois (*Am. Jour. Physiol.*, Dec., 1925, lxxv, p. 93), reported results from the injection of a series of six parathyroid extracts into thyroparathyroidectomized dogs. The extractives included acid alcohol and aqueous acid solutions. One solution was quite similar to Collip's. Tetany was prevented in parathyroidectomized dogs. In normal dogs the extract caused an increase in blood non-protein nitrogen, calcium, phosphorus, and in viscosity. The increase in phosphorus was a little delayed, following the rise in calcium.

Some time later, F. Dickens, E. C. Dodds, and D. T. Davies, of the Middlesex Hospital, London (*Biochem. Jour.*, Aug.-Sept., 1926, xx, p. 695), extracted temporarily active material from parathyroid glands by means of an acetone-picric-acid process. The hormone yields a picrate that is insoluble in water but soluble in 70 per cent. acetone. It resembles insulin in many of its reactions.

ANTIPHYMIN—Evidence is accumulating to show that the parathyroids are at the head of an endocrine mechanism that balances the thyro-adrenal-pituitary mechanism. Some interesting evidence to this effect is at present in the making. It has been found possible by the application of the fractionation procedures used in the separation of Anabolin* and hemopoietin from the liver, or in the separation of the four best-known anterior pituitary hormones, to divide the parathyroid product. It appears to be possible by these methods to free parathyroid solution from its calcium-regulating factor. The remainder contains a principle that evidently is the antithesis of the growth-producing hormone from the anterior pituitary. This preparation has been given the name "antiphymin" and, of course, is of only experimental interest.

Confirmation of this occurs in a note published by one of the workers in King's College, London, J. H. Thompson (*Brit. Med. Jour.*, May 9, 1931, i, p. 819), who has also succeeded in separating the blood-calcium-raising factor from a growth-inhibiting factor. He remarks:

"Extracts of parathyroid glands thus prepared have been injected intramuscularly into human subjects suffering from various types of carcinomata and sarcomata, including spheroidal-celled carcinoma, columnar-celled carcinoma, endothelioma, sarcoma, and glioma. The cases have been treated at the Soho Hospital for Women, the Westminster Hospital, and St. Bartholomew's Hospital. Some improvement has been noted, and the results are sufficiently encouraging to warrant a continuation of the investigation."

STANDARDIZATION—The two methods of standardization used most generally are those of Hanson and Collip. The Hanson method (*Jour. Am. Med. Assn.*, March 10, 1928, xc, p. 747) consists in producing an abnormal condition comparable to the condition that it is desired to treat in human beings, and in restoring this condition to normal by the administration of an active extract. Hanson's clinical unit is defined as 1/100 of the amount of extract required to raise the calcium level of the blood 1 mg. per 100 cc. in a 15-kg. parathyroidectomized dog within six hours. In the actual test, sufficient extract is given to restore the blood calcium to normal—an average rise of 3 mg.

The method proposed by Collip (*Jour. Biol. Chem.*, June, 1925, lxiv, p. 485) is based on the production of hypercalcemia, an abnormal condition, in normal dogs. The unit of potency of "Collip's hormone" is defined as "1/100 of the amount of extract which will produce an average increase of 5 mg. in the blood serum calcium of normal dogs of approximately 20 kilos weight over a period of fifteen hours." Physiological standardization is feasible because the blood-calcium-raising effect of a single injection of

extract is directly proportional to the size of the dose administered. Many dogs, at least ten, should be used in a test, and the animals should be maintained on a standard diet. (See also *Can. Med. Assn. Jour.,* May, 1931, xxiv, p. 646.) In my own work with Paracalcin,* many more dogs are found to be necessary, and it may be of interest to add that in the standardization of each batch no less than sixty-two blood-calcium estimations are made.

The most widely used method for the determination of serum calcium is Clark and Collip's modification of the Kramer-Tisdall method (*Jour. Biol. Chem.,* March, 1925, lxiii, p. 461).

There seems to be no publication discussing the comparative value of these two methods of standardization, so if one speaks in terms of Collip units the person standardizing by Hanson's method has no basis for comparison.

Another method of assaying parathyroid extract has been developed by H. W. C. Vines (*Brit. Med. Jour.,* Sept. 29, 1923, ii, p. 559). While the usual method is based on its effect on calcium metabolism, Vines' method is based on the capacity of the parathyroids to prevent intoxication by guanidine. Parathyroid is incubated with a known amount of guanidine in solution, and the amount of guanidine destroyed by the parathyroid is measured. Other tissues give similar reactions. The method is not in general use.

PARATHYROID BY MOUTH—For fully twenty years "parathyroid extract," a comparatively crude, defatted desiccation, has been used therapeutically. It is a tested remedy of obvious value, yet technically it cannot compare with any of the products previously mentioned. It is quite remarkable that oral therapy with this inelegant product, using a dosage ranging from 1/10 to ½ gr. daily, renders a service that is not so conveniently secured by injections of the perfected parathyroid hormone.

(In Chapter 24 the reader will find a record indicating that the same thing has occurred with thyroid extracts and that oral thyroid therapy accomplishes something that cannot be accomplished with thyroxin.)

The influence of "parathyroid feeding" also is capable of modifying a low blood-calcium index, and of causing a vital change in the capacity of the organism to heal ulcerative conditions (95). On the other hand, oral parathyroid therapy does not compare with the parathyroid hormone in the control of tetany, whether due to disease or produced experimentally.

Once again history repeats itself, and it is not hard to find evidences of it in the literature. The following is from an article by W. S. McCann, of Rochester, New York (*Jour. Am. Med. Assn.,* Dec. 6, 1924, lxxxiii, p. 1847):

"The use of parathyroid extracts has been recommended in the therapy of a large number of conditions. In most cases, such use rests on a very flimsy

foundation. . . . To devote the space required to enumerate the entire list of conditions in which the use of parathyroid therapy has been recommended does not seem justifiable, in view of the meager evidence of its value. It is the writer's opinion that there is no single condition for which the use of parathyroid therapy rests on a firm foundation of scientific proof except the use of autotransplants in tetania parathyreopriva."

Of course, it would be useless to develop a remedy and make it available to the profession for use in "tetania parathyreopriva," for, fortunately, this is one of the rarest of clinical findings. But there are many nutritional toxemias in which lime fixation is disturbed and in which the modification of this faculty may be utilized in a very real fashion. As this became more common knowledge, the same writer told quite another story about two years later. Quoting from McCann's second article (*Jour. Am. Med. Assn.*, Feb. 19, 1927, lxxxviii, p. 566):

". . . it is now possible to assert with confidence that we possess a therapeutic agent derived from the parathyroid gland which produces profound changes in the calcium metabolism. . . . At present there are definite indications . . . only in tetania parathyreopriva, infantile tetany, and in those pathological states in which low values of serum calcium content may be found."

The oral administration of desiccated parathyroid is in more wide-spread use to-day than at any time, and the reader will find great satisfaction from applying this method as suggested in Chapter 95.

PARATHYROID ACTIVE PRINCIPLES

ANTIPHYMIN (3)—An experimental fraction of parathyroid extract, free from the blood-calcium raising factor. It inhibits growth in immature animals.

PARACALCIN* (1A)—A stable aqueous solution of the active principle from beef parathyroids, standardized so that 100 units bring about an average increase of 5 mg. per cent. in the blood calcium of 20-kg. dogs within fifteen hours. In ampules of 0.5 cc., each containing 10 units—an average dose, which is given intramuscularly daily or every other day. Paracalcin is obtainable also in compressed tablets, each containing the equivalent of 0.5 cc. (10 units).

PARA-THOR-MONE (1A)—An aqueous solution of the active principle of the parathyroid glands made under the authority of the University of Alberta and standardized by Collip's method (on normal dogs). Each vial of 5 cc. contains 100 Collip units *(q.v.)*. Dosage: From 20 to 30 units repeated once or twice in twenty-four hours to relieve tetany, and from 10 to 20 units to prevent it. To control hemorrhage, from 10 to 15 units every thirty-six hours for several doses. *(Eli Lilly and Co.)*

PARATHYRIN (3)—The name originally given (1905) to the then hypothetical parathyroid hormone.

PARATHYROID EXTRACT (1B)—A parathyroid desiccation, one part of which is equivalent to ten parts of fresh gland. In tablets of 1/10 and 1/20 gr. Dose: From 1/10 to 1 gr. t.i.d.

PAROIDIN (1A)—The parathyroid hormone from beef in stable solution, standardized by Hanson's method (on parathyroidectomized dogs). Each cubic centimeter contains 150 Hanson units *(q.v.)*. Dosage: From 30 to 60 Hanson units intramuscularly every twelve hours for not more than ten days. *(Parke, Davis & Co.)*

17. THE PINEAL

Pineal Physiology — Epiphysin — Pineal Neoplasms — Timme's Pineal Myopathy—Pineal Products.

WHEN THE hypophysis turned out to be a real endocrine organ, it was quite natural for the delvers to wonder if perhaps the epiphysis might not also contain some more hidden endocrine dynamite, especially since this alleged vestigial remnant is not believed to have any demonstrable cerebral function.

The epiphysis, or pineal gland, is now accepted as an endocrine organ, but it has not attained a position of much interest because dyspinealism is so rare and obscure that it is almost impossible to diagnose it early.

PINEAL PHYSIOLOGY† has been determined largely from occasional clinical studies, but animal experiment has confirmed the ideas formulated. The scattered clinical records of pineal disease began to be analyzed from the endocrine standpoint, and soon it was evident that the pineal must be an endocrine structure, for it acted like one. For instance, a child in whom a teratomatous hypertrophy of the pineal was diagnosed, developed mentally so spectacularly that at five years he reasoned as would a young man with a predilection for ethics and philosophy! While such developments were interesting clinically, they were not determinable experimentally. Like the thymus, the pineal undergoes involution at puberty, hence the clinical results of dyspinealism are usually found in children.

Pineal feeding has been tried extensively in clinical practice as well as on animals. C. P. McCord, of Detroit (1914), reported that pineal feeding hastens the growth and maturity of tadpoles, paramecia, etc. W. N. Berkeley, of New York (1914), was enthusiastic about it as a means of improving conditions in certain classes of defective children; but this theory has fallen into desuetude.

The following brief comments enable us to gain an idea of what little is known about pineal physiology and endocrine relationships.

O. Marburg, of Vienna, believes that there is an antagonism between the hormone of the epiphysis and the hypophysis, and his opinion is shared by Biach and Hulles. This antagonism is probably the cause of the phenomena that frequently follow the castration of male animals. The pineal body atrophies, while the pituitary hypertrophies (*Arb. a. d. neurol. Inst. a. d. Wien. Univ.*, 1908, xvii, p. 217).

†As this is the only chapter on the pineal, it contains clinical as well as physiological discussions.

EPIPHYSIN—It was suggested by Berkeley (*Old Dominion Jour. Med. and Surg.*, 1913, xvi, p. 213) that the pineal appears to have the definite and important function of promoting the development of the human nervous system. How it acts to produce this remarkable result can be only surmised at present, but presumably the gland supplies a minute amount of an intracellular catalyst, occasionally known as "epiphysin," which may have something to do with the acceleration of the growth of the gray matter of the brain. Speaking of pineal therapy, Berkeley continues:

"In metabolic experiments upon young animals we were able only to hasten their somatic development, but when giving it to defective children we found that in most cases where there was no grave organic defect of the brain, the mentality showed a steady and gratifying improvement lasting over the whole period of administration. It has occurred to me also that pineal gland will not only hurry the slow mind of the defective child, but that it will also arrest or retard many cases of premature senile decay of the mental faculties, thus making it a physiological stimulant or food for the failing powers of old people who yet have no grave organic disease. I have had encouraging success so far, and I hope to report shortly a long series of cases of this kind showing the successes and limitations of the treatment."

This promised paper appeared some months later, outlining the experiments of C. L. Dana and Berkeley (*Med. Rec.*, 1913, lxxxiii, p. 835). These were: (1) The nucleoproteids and entire pineal extracts were obtained and injected into the veins to test the effect on the blood-pressure; (2) they were also injected into young rabbits and guinea-pigs for a long time to determine the effect on nutrition; (3) the whole gland was given to young animals; (4) the whole gland was given to defective and retarded children. For nearly eight months the investigation was confined almost exclusively to feeding experiments. The authors gave the gland to guinea-pigs and rabbits, and to certain selected children—if possible under 8 or 9 years of age—and to children who seemed to present cases of simple retardation without notable anatomic defect and without epilepsy. Children in the retarded grades of the public schools were used for this purpose, as well as private cases at the New Jersey Training School for the Feeble-Minded at Vineland. The gland was fed to twenty-one children, who were studied and compared with twenty-one controls.

Many an extract has been made from the pineal since the work of Dana and Berkeley, but pineal therapy has not justified the amount of effort put into its perfection. The extract is costly, for it is said that it takes the pineals from five thousand beeves to make one pound of the finished concentrate.

Recently, at Johns Hopkins University, S. J. Weinberg and A. F. Doyle

series of experiments with pineal extracts on the growth of mice. No effects were noted on either growth or the sexual apparatus.

According to a personal communication from Prof. Paul Werner, Vienna gynecologist, pineal extract is available as a means of overcoming excessive libido. He writes:

"In view of the frequent connection between diseases of the pineal and precocious puberty, also excessive libido, these cases here in Vienna are treated with prolonged courses of pineal extract, and very satisfactory results have been obtained. I believe it proper to suggest this treatment for your clinical test."

PINEAL NEOPLASMS—Although various pineal neoplasms (usually teratomata) have been recorded, they are very rare. The ordinary symptoms are those of pressure, as of any brain tumor. Local neighborhood signs are produced by pressure on the cranial nerves, especially ocular deviations and occlusion of the aqueduct of Sylvius, with marked ventricular pressure causing choked disc, severe headache, and vomiting of the projectile type.

The endocrine symptoms are unusual or precocious growth and development, both mental and sexual. Hypergonadism rarely follows pineal tumor in girls, but there is abnormal growth of the genitals in boys. The secondary sex characteristics (hair, voice, etc.) occur years before the normal time, and the intelligence quotient is much higher than normal.

The treatment of pineal tumors is hopeless, for surgery is impossible, although experimental pinealectomy has been done. X-ray therapy may help temporarily. Pineal organotherapy is not effective.

TIMME'S PINEAL MYOPATHY—Some years ago Walter Timme, of New York (*Arch. Int. Med.*, Jan., 1917, xix, p. 79), described a form of muscular dystrophy which he connected with dysfunction of the pineal gland and called "pineal myopathy." The diagnosis was based on the discovery of a condition of pineal calcification (visible by the X-ray), mental precocity, and a progressive asthenia with occasional muscular atrophy. Several cases have improved following the use of pineal extract (1/5 gr. t.i.d.), thus confirming the tentative diagnosis. This is, however, about the only acceptable use for pineal therapy.

PINEAL PRODUCTS

EPIPHYSIN (3)—The name given to a principle alleged to be the essential pineal hormone. The product is not yet isolated.

PINEAL EXTRACT (2)—A desiccation of fresh beef pineal, each part equal to about eight parts of fresh material. Dose, indeterminate—from 1/10 to ½ gr. t.i.d. over long periods.

18. THE PITUITARY

I. ANTERIOR LOBE: *The Growth Hormone: Accretin,* Phyone, Tethelin —The Estrous Hormone: Apestrin,* Prolan, Rho-one—Clinical Utility— The Antestrous Hormone: Prolan-B, Rho-two—The Luteinizing Hormone · Aplutin*—The Thyreotropic Hormone.* II. POSTERIOR LOBE: *Hypophysin, Infundibulin, Pituitrin—Standardization — Pituthymin,* Thymophysin — Oxytocin and Vasopressin—Retrospect—Pituitary Products.*

MORE SURPRISES have been encountered in the study of the pituitary body, or hypophysis cerebri, than of any other organ of internal secretion. Not more wonderful, perhaps, nor more clinically useful; but numerically more. Already no less than seven active principles have been separated from the pituitary, at least four of which have been offered to the profession for clinical use.

This gland, first noticed by Vesalius in 1543, was not suspected of any such functions as we now connect with it. In fact, it was not until 1895 that the true endocrine nature of the pituitary was sensed by G. Oliver and E. S. Schafer, of Edinburgh. Gradually its physiological importance grew, first one function being connected with it, then another, until now a veritable avalanche of well-substantiated data has overwhelmed the profession—so much information that only a small part of it is as yet clinically appreciated.

Before proceeding to a consideration of these stirring developments, it may be proper to remind the reader that the pituitary is a small organ (in man, the size of a hickory-nut) lying in the bony cup known as the sella turcica at the base of the skull, just above the sphenoidal sinus.

Seventeen years ago, I wrote the following ("Practical Hormone Therapy," London, Baillière, Tindall & Cox, 1914, p. 288):

"Embryology has taught us that the pituitary body develops from two dissimilar cell aggregates, the one part from the roof of the mouth (Rathke's pouch), and the other from the neural canal or ventricle. The epithelial part is now known as the 'anterior lobe,' while the smaller neural portion is called the 'posterior lobe,' and the 'infundibulum.'

"Physiology has explained that the functions of the different portions of the pituitary are quite diverse, and histology shows that their structure is also different, the anterior or glandular portion having a yellow or reddish-gray colour, and showing microscopically well-formed columns of cells; while the smaller posterior lobe is of a whitish colour, and under the microscope shows much connective tissue, fibres, neuroglia, and eosinophile cells. Between the lobes, and connecting them, is a third portion, the so-called 'pars nervosa' or 'pars intermedia.' . . . Not so long ago the pituitary was called by the French *l'organe énigmatique,* but now that the riddle is being solved, it is almost as hard to believe the truth concerning the importance of this

organ and the action of its extracts as it is to realize how ignorant we have been."

And how really ignorant we were when we thought we knew so much about this gland! Let us see.

I. THE ANTERIOR LOBE

This portion of the pituitary gland represents more than seven-eighths of its weight. It is the vital part of the organ, clearly glandular in character, yet until the last three or four years not so well understood as the posterior lobe, especially as a source of endocrine principles.

Misunderstandings have occurred about the status of this organ, and the reader may be amused or concerned, as the case may be, by noting some of the confusion that has been recorded (see pages 53 and 440).

A rather complicated situation has resulted from the independent investigations carried on by numerous research workers. Although four hormones have been separated from the anterior pituitary, experiments upon animals have shown no less than eleven distinct activities of this versatile organ. These are listed in an article by E. P. Bugbee and associates, of Detroit (*Endocrinology,* Jan.-Feb., 1931, xv, p. 41), as follows:

"(1) Stimulation of growth; (2) stimulation of sexual development and ripening of follicles, resulting in ovulation; (3) stimulation of lutein cells, resulting in prevention of ovulation by imprisoning the ova; (4) stimulation of sexual development by a substance that can be given by mouth, in distinction to 2, which has very little effect when given by mouth; (5) stimulation of metabolism by increasing the specific dynamic action of food substances; (6) stimulation of the thyroid gland; (7) lowering of gaseous metabolism; (8) stimulation of the water intake and output; (9) stimulation of lactation; (10) lowering of non-protein nitrogen in blood; (11) initiation of the bleeding of menstruation."

It must suffice here to stress chiefly the first three and give only casual attention to some of the others.

THE GROWTH HORMONE: ACCRETIN,* PHYONE, TETHELIN—In 1916, T. Brailsford Robertson reported his experimental research in the University of California on the growth of white mice. According to him (*Jour. Biol. Chem.,* March, 1916, xxiv, p. 385), 0.125 Gm. of fresh anterior pituitary lobe tissue given daily to each animal retarded the growth in the earlier part of the third growth cycle, but in the latter part, *i.e.,* from the twentieth to the sixtieth week after birth, it caused their growth to be so markedly accelerated that they not only caught up to the normals, but actually, when about 1 year old, surpassed them in weight. Robertson (*ibid.,* p. 397) prepared a substance named "tethelin," which is precipitated by the addition

of ether to the concentrated alcoholic extract of dried anterior lobes. The effects of tethelin on the growth of rats are similar to those of whole anterior lobe pituitary. The average content of tethelin in each anterior lobe was believed to be 10 mg.

This substance eventually was made available to the profession under license of the University of California, but it has not attained any great vogue. Because of its unstable nature, it was found necessary to keep the powdered concentrate in vacuo, and this interfered greatly with its exploitation.

However, a mass of additional data has been accumulated by H. M. Evans and other workers in the University of California, also by P. E. Smith, of Stanford University. In a summary of this work (*Jour. Am. Med. Assn.*, Nov. 3, 1928, xci, p. 1337), H. M. Evans and M. E. Simpson refer to some earlier work in this country:

"In 1923, P. E. Smith (*Anat. Rec.*, 1923, xxv, p. 150) in this laboratory showed that nature gives us a partial separation of the eosinophilic and basophilic cells in their distribution in the pars anterior of the bovine gland, a dark red central strip indicating an area of relative abundance of the basophiles when compared with peripheral zones in the gland. Smith administered extracts made from these two portions of the gland to hypophysectomized tadpoles and was able to demonstrate relatively more of the growth effect in the cortical zone extracts."

In 1927, W. G. Downs, Jr. (*Ann. Int. Med.*, Dec., 1927, i, p. 412), made a study of the relationship between the endocrine glands and the development of the dental mechanism. In his experiments on dogs he found that the pituitary gland had no effect on dental development, but he obtained some interesting systemic results. He used five litters of four puppies each. In each litter one dog was fed anterior lobe extract, one posterior lobe, and one whole gland, while the control animal received a normal diet. In the animals that received anterior lobe extracts, the tibias were notably larger and showed greatly delayed epiphyseal closure as contrasted with the controls. He noted that the development of the long bones is constantly and progressively greater in those animals receiving anterior lobe extract, intermediate in the controls, and smaller in the animals on posterior lobe extract.

In reviewing these researches, Leslie F. Hewitt, of the London Hospital Medical School (*Biochem. Jour.*, Aug.-Sept., 1929, xxiii, p. 718), summarizes the effects that have been ascribed to the anterior pituitary, and reports on his own work in which he attempted to repeat and amplify that done before. He found it possible to obtain extracts of anterior lobes of pituitary glands capable of producing:

(1) A growth-promoting effect (filtered alkaline extracts).
(2) Growth-promoting and estrus-inhibiting effects (unfiltered alkaline extracts).
(3) Premature maturity and ripe follicle-producing effects (acid extracts treated with kaolin, etc.).

These three different physiological effects can be produced by anterior pituitary extracts prepared in different ways. Thus laboratory evidence confirms the previously suspected existence in the anterior pituitary of hormones that control growth and the female reproductive cycle.

Hewitt considers it possible that the growth-promoting extract has two effects, namely, to stimulate growth and to stimulate the thyroid gland. He quotes P. E. Smith (*Anat. Rec.*, 1922, xxiii, p. 38) as having shown that the thyroid is affected by the anterior pituitary lobe, as is proved by the fact that ablation of this lobe in tadpoles is followed by atrophy of the thyroid. Further, anterior pituitary deficiency results in depression of metabolism, temperature, etc., and hypertrophy of this portion of the pituitary is frequently associated with increase in the activity of the thyroid. It has been observed that growth ceases and that there is a rapid fall in weight as soon as injections of anterior pituitary extract are discontinued. This may be due to the stimulation received by the thyroid through the growth-promoting extract. From this, Hewitt concludes tentatively that perhaps anterior pituitary medication might improve intractable cases of hypothyroidism. From the clinical point of view, I can add that he is quite right, and the reverse is just as true. There is a close cooperation between these two glands.

More recently H. B. Van Dyke and Z. Wallen-Lawrence, of Chicago (*Jour. Pharmacol. and Exper. Therap.*, Dec., 1930, xl, p. 413), apply the term "phyone" (Greek, *phyo*, I cause to grow) to the growth hormone of the glandular portion of the pituitary. Their report deals with a method of preparing a potent, non-irritating phyone extract, which is quite complicated and cannot be abstracted.

The authors then give a method for assaying phyone, which so far is possible only by biological methods in which they use hypophysectomized female rats weighing from 80 to 100 Gm. Hypophysectomy was considered complete if growth ceased and the estrus cycles disappeared. The injections in doses proportional to each animal's weight are made subcutaneously once a day for three days. If the preparation is potent, the weight of the group is significantly increased twenty-four hours later. Hypophysectomized rats show a greater response to phyone than do normal adult rats. While it is possible to increase the weight of an operated animal 16 per cent. after four daily injections of phyone, and while weight increases of from 10 to 12

per cent. are frequently obtained in animals even three or four months after hypophysectomy, after that period animals that have previously responded often do not show an increase in weight following the administration of the hormone. Age appears to be a factor in the reaction of the hypophysectomized rat just as it is with the normal rat.

My own preoccupation with this subject has been largely clinical and is based on my study during eighteen years of the endocrine responses of a series of developmentally abnormal children in whom growth defects were a part of the picture. Many times therapy with anterior pituitary substance or a combination of anterior lobe with thymus and thyroid (46) was followed by increases in height; in fact, this is almost the rule, provided these children are responding in other ways, thus showing that such treatment is indeed indicated.

In the effort to improve the means at our disposal, some of the methods outlined in the literature were used to concentrate the material employed and, briefly, a product known as Accretin* (Latin, *accresco,* I grow, or add to) was prepared from the anterior lobe and the thymus (but no thyroid).

At this time (1929), interest in the laboratory side of this subject was increasing, and so growth experiments on animals were begun. The pituitary concentrate, each gram of which is equivalent to 12 Gm. of fresh anterior lobe, was fed (*not* injected) to a series of immature rats, using as controls other animals of the same sex and weight from the same litter. It was found that the average rate of growth could be increased 100 per cent. in periods ranging from ten to fourteen days. A rough mathematical measure of the potency of the extract was thus available, the "growth unit" being a factor based on the amount of extract used and the time required to double the growth rate (not the weight). It was also found that feeding much larger amounts to mature animals caused negligible increases in their growth.

Accretin is, therefore, a clinically known-to-be-potent growth-stimulating substance, the experimental results of which have confirmed its potentialities. It is suggested as a means of increasing stature in preadolescent young persons (verified by epiphyseal X-ray pictures) whose shortness is characterized by a reduced upper and an increased lower measurement (with the pubis as the center point), and whose span exceeds their height. It is very evident that the effect of this product must be catalytic or homostimulative, for the comparative per-kilo dosage is but a fraction of that used in the animal tests. The usual dose of Accretin is 20 gr. or more a day for several months. The greatest growth increase reported is 6½ inches in fourteen months (in a male, age nineteen).

THE ESTROUS HORMONE: APESTRIN,* PROLAN, RHO-ONE—In other chapters there has been outlined information regarding a series of active principles called estrins, which are obtainable from the follicular fluid and the ovarian tissue (11) and from the placenta (19). It appears that a very similar product originating in the anterior lobe of the pituitary plays an important part in the initiation and production of the ovarian reproductive cycle. So marked is this ovarian influence that ovulation actually has been observed by C. W. Bellerby, of Middlesex Hospital, London (*Lancet,* June 9, 1928, ccxiv, p. 1168), following injections of anterior lobe extracts.

This anterior pituitary principle, however, exerts its influence indirectly; that is, by the initiation on the part of the ovary of the production of estrin. In this respect it differs from folliculin or Plestrin, for these true estrins are active even in the spayed animal, while Apestrin is not. It has been shown in various laboratories that there is an anterior pituitary estrin capable of promoting even more vital ovarian and luteal changes. F. A. E. Crew and B. P. Wiesner, of the University of Edinburgh (*Brit. Med. Jour.,* April 26, 1930, i, p. 777; *Edinburgh Med. Jour.,* Feb., 1930, xxxvii, p. 73), whose work in the separation of various active principles from the placenta is referred to in the next chapter, were among the first to distinguish two separate products of this nature, one of which is called "Rho-one," the estrogenic factor that stimulates the first phase of ovarian activity—the secretion of estrin, the follicle maturation, and the formation of corpora lutea—which is characterized by the production of estrus. The other, known as "Rho-two," is believed to arouse the second phase of ovarian activity, the luteal endocrine activity, and to maintain the luteal function. These appear to balance each other and are often considered together. They are common to both sexes and stimulate the primary sexual organs. They are the activators of sexual development at puberty. Since it has been found possible to obtain extracts that contain both sex hormones but not the growth factor, it follows that the growth and sex hormones are "distinct and separable."

Evans and Simpson (*Am. Jour. Physiol.,* July, 1929, lxxxix, p. 381) agree with Wiesner and Crew that there are two separate sex hormones in the anterior pituitary, but other workers (*Endocrinology,* Jan.-Feb., 1931, xv, p. 41) believe that there is no definite proof that these two factors really constitute two hormones, although they admit the two functions of this "master sex hormone." The Germans call this "the antepituitary hormone discovered by Zondek." (It is difficult to give proper credit for endocrine advances, but most investigators concede to Wiesner and Crew priority over Zondek, while H. M. Evans postulated this principle some years ago.)

The anterior lobe of the pituitary is well named "the motor of the sexual function." It has a stimulating effect on the ovary even in the child, but it influences other parts of the sexual apparatus only by way of the ovary.

The German workers speak of the "hormone-*A*" of the anterior lobe of the pituitary, which precipitates the maturation of the ovum, and "hormone-*B*," which causes luteinization. In addition, a general growth hormone and a metabolism hormone are postulated. It has been found in the course of German research that the male pituitary secretes approximately the same amount of hormones as the female. The hormone-*A* is produced in three times the quantity of the hormone-*B*. The pregnancy test of Aschheim and Zondek† is based on the demonstration of this hormone in the urine.

For some time it was difficult to understand these seemingly conflicting points, but as a result of Wiesner's work it was found that the first of these two products (Rho-one) is destroyed by boiling for one minute, while the second (Rho-two) is not, thus facilitating their separation.

Various names have been given to the anterior pituitary estrin: Apestrin,* Homhormone, and Prolan. Apparently this latter is the only one at present available. It is physiologically standardized by its estrus-producing effects, and it is recommended therapeutically as a means of mobilizing the ovarian hormone. The activity of this German product is standardized in rat units (not Doisy units, however), and the solution is administered in various doses ranging from 100 to 300 rat units daily. The indications are hypogonadism in both sexes, but especially ultimate degrees of amenorrhea and infantilism in the female.

In a more recent communication from Berlin, Bernhard Zondek and W. Berblinger (*Klin. Wchnschr.*, June 6, 1931, x, p. 1061) point out that the hormones of the anterior lobe of the pituitary are the superordinated, general sex hormones. These workers make the important point that they are primary, while the sex hormones proper are secondary. The follicle-

†The Aschheim-Zondek test for early pregnancy deserves mention here. It is essentially an endocrine reaction, and, because of the reliability of its results, it is a real clinical accomplishment. (If the fetus is living, the accuracy is conceded to be from 98 to 99 per cent.) The procedure is as follows: Subcutaneous injections of the morning urine of a woman suspected of being pregnant are made into immature female mice. If the woman is pregnant, the injection is followed by swelling, congestion, and hemorrhage of the ovaries, together with the premature maturation of the follicles—changes visible to the naked eye. Five immature female mice (3 weeks old, weighing 12 Gm. each) are used for each test. The mice receive six injections: three on the first day and three on the second. Single doses are: 0.2 cc. for mouse No. 1; 0.25 cc. for mouse No. 2; 0.3 cc. for mouse No. 3 and mouse No. 4; 0.4 cc. for mouse No. 5. The mice are killed one hundred hours after the first injection. Many workers use only one mouse for each test and report a high percentage of results with animals from 3 to 5 weeks old, weighing from 6 to 10 Gm. each.

maturation hormone (*A*) is produced by the direct effects of the pituitary on the follicle apparatus of the ovary. This later results in the formation of the female sex hormone (folliculin), while the luteinizing hormone (*B*), which is also produced in the anterior lobe, causes the formation of the corpus luteum hormone in the corpus luteum. It is the functional rhythm of the anterior lobe of the pituitary that determines the rhythm of the sexual function; it also initiates the proliferation and functioning of the uterine mucosa and thus creates optimal conditions for the nidation of the fertilized ovum. These German investigators rightly insist that *without the hormones of the anterior lobe of the pituitary there would be no sex hormones.*

In view of the fact that such potent estrins can be obtained from the placenta, some research work has been done to determine whether or not the placenta merely stores the estrin produced by the anterior pituitary. Possibly this is the case, but E. Philipp, of Berlin (*Zentralbl. f. Gynäk.*, Dec. 6, 1930, liv, p. 3076), believes that this pituitary product is separate—as had been suggested before—but that it also takes an active part in the production of the corresponding placental estrin. As J. B. Collip, of Montreal (*Can. Med. Assn. Jour.*, June, 1930, xxii, p. 764), puts it:

"Philipp is inclined to believe that the placenta does not merely collect and store the hormone produced by the anterior hypophysis, but takes an active part in the production; but he maintains that the flooding of blood and urine with the hormone takes place so early in pregnancy that it must be ascribed to hypophyseal, not to placental, activity."

CLINICAL UTILITY—At present there are only limited clinical possibilities from this research. Few of these products are likely ever to be available in dependable form. Apestrin,* the name given by me to this anterior pituitary estrin, is virtually an experimental product, and it seems that it may have to remain so for three reasons: (1) It is most expensive, (2) we already have in Plestrin* a decisively active product apparently identical in its trophic effects (see Chapter 19), and (3) the best way to get clinical good from the anterior pituitary estrin is to encourage its production *in the patient.* This leads to other forms of organotherapy, and, when conditions arise in which such an influence is missing, the attempt should be made to balance all the factors involved—pituitary, thyroid, ovarian, etc. (80). This explains many of the empirical successes of the past years, while it gives an experimental background that confirms our earlier suspicions regarding the need for pituitary therapy in ovarian dysfunction. (It is now claimed that primary amenorrhea responds better to pituitary than to ovarian preparations.)

Before we leave this subject, some comments by W. Langdon Brown, the well-known London endocrinologist, may be interesting. In stressing the

balance that exists between these various hormones, he refers to the familiar fact that the anterior lobe contains both eosinophile and basophile cells. This is related to the two outstanding principles that have to do with growth and sexual development. Langdon Brown then suggests that one association exists between the eosinophile cells and growth, and another between the basophile cells and the gonads. He says (outline) (*Clin. Jour.*, June 4, 1930, lix, p. 265):

That growth precedes sexual maturity is presumably due to the early predominance of the growth hormone. The retardation of sexual maturity in the interest of somatic growth is similarly determined by the action of the pineal body and the thymus gland. Growth is probably determined by the predominance of the eosinophile cells, and, when the basophile cells are able to assert themselves over the eosinophile cells, puberty occurs.

It is noteworthy that overactivity of the anterior pituitary, as expressed in basophilic adenomas, tends, like adrenal cortical tumors, to produce virilism.

Accordingly, it is necessary to consider dwarfism without sexual hypoplasia, as distinct from infantilism with defective development of the eosinophile cells of the anterior pituitary. Further, just as basophilic overgrowth of the anterior pituitary or adrenal cortical tumors may produce sexual development always tending to virilism, so lack of anterior pituitary (presumably eosinophilic) or of adrenal cortex may lead to dwarfism, with premature senility (progeria).

A whole volume might be written on this subject—there is so much of interest—but it must suffice to add a point or two regarding the relation between the histology and the endocrine functioning of the anterior pituitary lobe. This also is discussed by Philipp, who states that in children the pituitary shows not only undifferentiated main cells but also chromatophilia and especially eosinophilia, which increase with the age. In mice, transplantation was followed by a moderately strong reaction. In adults outside of pregnancy, the pituitary is found to contain many eosinophile cells and gives a marked anterior pituitary reaction for pregnancy. Extracts from the pituitary of pregnant women do not show any action on the ovaries of mice. The main cells and pregnancy cells of the pituitary cannot be shown to have any influence on the ovaries of infantile mice after implantation—in contradistinction, of course, to the extracts from glands from non-pregnant sources.

THE ANTESTROUS HORMONE: PROLAN-*B*, RHO-TWO — There can no longer be doubt about the presence of a "balancer," in the anterior lobe of the pituitary, of its potent estrin. This has been referred to before, but it must be added here that the pituitary antestrin called by Wiesner "Rho-two" and by Zondek "Prolan-*B*" is evidently the physiological activator of progestin or the corpus luteum hormone, which is the antithesis of the

estrins or female sex hormone. This, then, really belongs with our consideration of the luteal hormone (11).

THE LUTEINIZING HORMONE: APLUTIN*—Increasing interest is being shown in the luteinizing principle, or "the third hormone from the anterior pituitary." This substance, to which the name "Aplutin"* has been given, stimulates the lutein cells and apparently is comparable with the product known as lutin, separated from the corpus luteum (11). By means of pyridine, this luteinizing hormone has been separated from desiccated anterior pituitary by H. L. Fevold and his associates in the University of Wisconsin (*Am. Jour. Physiol.*, May, 1931, xcvii, p. 291). Of it they say:

"An aqueous pyridine extract of the dried anterior lobe produces precocious sexual maturity together with tremendous luteinization of the ovary."

Some more confirmatory research work is now in process at Johns Hopkins University (see *Bull. Johns Hopkins Hosp.*, Aug., 1931, xlix, p. 106). This luteinizing hormone already has found a place in practical therapeutics, although at present it is being used largely in an experimental way.

THE THYREOTROPIC HORMONE—In Wiesner's article (*loc. cit.*), attention is called to a fourth hormone from the anterior lobe of the pituitary, which was shown by numerous experiments to act upon the thyroid. One of the effects of this principle manifested itself in the metabolic rate, but this was proved to be ineffective in thyroidectomized animals. This influence is of special importance in our consideration of endocrinopathies of a developmental nature, which naturally would involve both the thyroid and the pituitary (46).

In this connection, another point deserves mention: In his monographic treatise on development and growth, F. Gudernatsch, now of New York (Max Hirsch's "Handbuch der inneren Sekretion," Leipzig, Curt Kabitzsch, Vol. II, Fascicle 8, 1930, p. 1698), separates the terms "growth" and "differentiation" because these two processes are not identical, even though they are associated. He finds a correlating mechanism existing between the pituitary and the thyroid. While, according to Gudernatsch, the anterior pituitary must be looked upon as the typical growth-promoting gland, it also influences differentiation. On the other hand, the thyroid is mainly concerned with differentiation; yet each complements the other's functions. It is now suggested that the fourth anterior pituitary hormone, the thyreotropic hormone so named by Wiesner, is responsible for this phase of development through and with the thyroid, thus adding additional weight to the suggestion made by me in 1917 that thyroid should be given with pituitary

(anterior) in cases of pituitary infantilism, while pituitary should be given in thyroid cases with developmental stigmata.

This fits in nicely with the clinical conclusions stated some years ago by G. Y. Oliver, of London (*Prescriber,* Feb., 1924, xviii, p. 68):

"Now the relation between the thyroid and the anterior pituitary is more complex than would at first appear. My observations lead me to believe that if the secretion of the anterior pituitary tends to fail, the thyroid has a tendency to assume a dual function—that of the pituitary as well as its own. . . . It is interesting to note that in nearly all adult cases of hyper-anterior pituitarism the sella turcica is comparatively large, while in hyperthyroid cases the sella turcica is very narrow and shut in. . . . In other words, in a child born with an overactive thyroid, the anterior pituitary will have less demand on it and will not enlarge so quickly, with the result that the adult pituitary fossa will be small. If, on the other hand, the child is hypothyroid, the anterior pituitary will oversecrete and the pituitary fossa in the adult will enlarge accordingly."

II. THE POSTERIOR LOBE

When, back in 1895, workers in the University of Edinburgh were studying the influence in the laboratory of numerous glandular substances, they made the first important discovery regarding the physiological action of extracts of the pituitary body. G. Oliver and E. S. Schafer (*Jour. Physiol.,* 1895, xviii, p. 277) found that watery or saline extracts of this tissue, even when boiled, raised the blood-pressure and constricted the peripheral blood-vessels. Three years later, W. H. Howell, of Baltimore, observed that the property of increasing blood-pressure was confined to the extracts of the posterior lobe and that, when the blood-pressure was raised, the pulse was slowed. In 1901 Magnus and Schafer found that this extract was markedly diuretic, and in 1906 Herring and Schafer observed that, although the infundibular extract constricts the arteries in general, it dilates those of the kidneys, and is diuretic.

Unknowingly, these workers were really exploring the posterior lobe of the pituitary rather than the gland as a whole. Within a few years H. H. Dale, then of the Wellcome Research Laboratories in Dartford, Kent, who happened to be studying ergamine and similar substances with a uterotonic influence, found himself suddenly interested in the pituitary. As he knew of the previous reports of the musculotonic influence of pituitary extract, it was being considered in his studies. He prepared a pituitary extract, the experimental influence of which was marked (*Jour. Physiol.,* 1906, xxxiv, p. 163). Referring to its essentially muscular effects, Dale said later (*Proc. Roy. Soc. Med.,* 1914, vii, p. 34):

"There is an increasing body of evidence which indicates that the pituitary principle acts on plain muscle more by increasing its sensitiveness to normal stimuli than by acting as a direct stimulant (cf. v. Frankl-Hochwart and Fröhlich). In the normal person it causes no rise of blood-pressure; in the experimental animal with high blood-pressure it may even cause a fall. Yet, when the pressure is artificially lowered, as by cutting off the vasomotor centre, the tonic effect of pituitary extract on the arteries is great and prolonged."

It was this presumed increased sensitiveness to normal stimuli that led to the first use of the product (called "Infundibulin") in labor. W. Blair Bell, of Liverpool, who at first was working independently and later cooperated with Dale, had the vision to sense the obstetric possibilities of this substance (see *Brit. Med. Jour.*, Feb. 27, 1909, i, p. 517; *ibid.*, March 6, p. 592). Late in the same year (*ibid.*, Dec. 4, 1909, ii, p. 1609), Blair Bell announced "the therapeutic value of the infundibular extract in shock, uterine atony, and intestinal paresis." Thus another epoch-making advance had been accomplished.

HYPOPHYSIN, INFUNDIBULIN, PITUITRIN—There are scores of posterior pituitary extracts now in wide use along exactly the same lines predicted by Blair Bell. Three of them deserve special mention from the point of view of priority. Hypophysin, perfected in Germany independently by S. Hertzberg and H. Fühner, was a salt of the posterior pituitary substance—hypophysin sulphate, offered in a standardized 1:1000 solution. But it was later found that hypophysin was a mixture containing several active principles (Fühner himself claimed to have found no less than four), and that the acceptable way to standardize it was physiologically and not chemically.

Infundibulin (now known as Infundin) undoubtedly was the first product of this nature to be used, while pituitrin was the first product made available to the profession in a general way. This latter is still in wide use, and is available in two strengths, surgical and obstetrical. Many clinical references to its value will be found in Section IV. The standardization of pituitrin is a matter of interest and importance.

STANDARDIZATION—Apparently there is no chemical test sufficiently specific to form the basis for a good quantitative determination of the potency of a posterior pituitary preparation. On the other hand, there are several biological methods based on its physiological action. The most widely used quantitative method is that based on the oxytocic action on the isolated uterus of the virgin guinea-pig. This method was originated in 1912 by H. H. Dale and P. P. Laidlaw (*Jour. Pharmacol. and Exper. Therap.*, 1912, iv, p. 75), and has been revised to the final form now appearing in the U.S.P. X.

The standard solution for the assay is prepared from a standard acetone-extracted pituitary desiccation suggested by Carl Voegtlin, of Washington, D. C., to the Health Committee of the League of Nations at Geneva in September, 1925. The guinea-pig from which the uterus is taken should weigh preferably between 200 and 300 Gm. The uterus is suspended in an apparatus designed for the measurement of the activity of the isolated smooth muscle of mammals in oxygenated Locke-Ringer solution at a uniform temperature of from 37° to 38° C. The solution to be tested is added to the Locke's solution. Several successive doses of the standard should be used as a basis for comparison before adding the unknown.

In the U.S.P. X, it is stated that the acceptable pituitary solution called "Liquor Pituitarii" contains

"The water-soluble principle or principles from the fresh posterior lobe of the pituitary body of cattle, 1 cc. having an activity upon the isolated uterus of the virgin guinea-pig corresponding to not less than 80 per cent. and not more than 120 per cent. of that produced by 0.005 Gm. of the standard powdered pituitary."

Now that vasopressin (*q.v.*) has been separated as a distinct entity, the measurement of the pressor response to pituitary extracts is necessary. The oxytocic and pressor factors exist in equal amounts in the standard pituitary powder, and so assay of total posterior pituitary is adequate when the oxytocic response is measured. Pressor action is measured in either cats or dogs. A quantitative method using dogs was developed by H. C. Hamilton (*Jour. Am. Pharm. Assn.*, 1912, i, p. 1117).

PITUTHYMIN,* THYMOPHYSIN—Years passed by while these accomplishments were being assimilated by the profession. Thousands of experiments were carried out, tens of thousands of patients were treated, hundreds of papers were published, then two more "big stories" broke—one in Europe, the other in this country. The first of these had to do with a modification of the posterior pituitary solution for use in labor.

At the Congress of the German Gynecological Society in 1925, it was reported by Nikolaus Temesváry, of Breslau (*Zentralbl. f. Gynäk.*, Feb. 6, 1926, l, p. 322), that a certain type of thymus extract, when combined with posterior pituitary solution, changed the response to the latter from spastic uterine contractions to rhythmical, broken contractions that were much more like the physiological labor pains. According to this writer, a pituitary-thymus extract (later known as Thymophysin) could be used for the same purpose as the posterior pituitary oxytocic principle, but with the important difference that it could be administered with safety during the

first stage of labor. Liquor Pituitarii ordinarily is contraindicated during this stage because it may produce prolonged uterine contractions, which sometimes pass into spasm and cause injury to the mother and even death to the child. Another peculiar point noted by Temesváry was that if this preparation is given before labor actually has started, that is, if the uterus has not been "sensitized," the mixture does not produce this uterotonic effect. But, when these conditions are complied with, prompt dilatation of the os is promoted. Further, in contrast to the short duration of the influence of pituitary, that of the combination lasted for several hours, extending even to the delivery of the placenta.

When, at the request of a number of friends who had heard of this idea, I perfected a similar product called Pituthymin,* it began to be used in this country. Soon there came the customary denials and comments. In the meantime, numerous papers speaking well of this method have appeared in the foreign and domestic literature.

Many hundreds of physicians are now using pituitary-thymus solutions in labor with much more satisfactory results than those obtained with the previously used solutions. But the point that is admittedly disconcerting is that as yet no satisfactory explanation has been given why the combination of the thymus and posterior pituitary modifies the influence of the latter in the way that it undoubtedly does.

OXYTOCIN AND VASOPRESSIN—The other accomplishment is known as "the splitting of pituitrin" into its two dissimilar physiologically active components. This is another triumph of the principle of fractionization, and was accomplished by Oliver Kamm and his associates in Detroit (*Jour. Am. Chem. Soc.*, Feb., 1928, I, p. 573). These workers found that the posterior lobe of the pituitary contains two principles (chemical twins) which, while resembling each other in chemical constitution and even in molecular magnitude, do not act alike. One of them stimulates the contraction of muscle, while the other raises the blood-pressure.

The first of these, oxytocin (also known as Pitocin), has a marked musculotonic effect and the same peculiar affinity for uterine muscle that has been noted during the years of experience with pituitrin. In other words, this effect is particularly marked when the uterus is sensitized as it is at the end of normal gestation. It has no effect on blood-pressure, thus making it more suitable for use in labor where the pressor effect is contraindicated, as in the case of uterine inertia with hypertension or even eclampsia.

The other hormone, known as vasopressin (also called Pitressin), contracts the blood-vessels, thereby increasing the arterial tone. But it has no

effect on the uterus. There are occasions when the pressor effect is desirable to prevent or control operative shock and the oxytocic effect is to be avoided as in the case of pregnancy requiring surgical treatment for some incidental condition. It is useful in diabetes insipidus during pregnancy, for this pressor principle also happens to be an antidiuretic.

RETROSPECT—It must be admitted that it is quite possible that some of these principles presumed to originate in the pituitary do, in fact, arise elsewhere. It may be also that some of the closely similar principles found in other tissues, *e.g.*, the placenta, really come from the pituitary but are stored elsewhere. For this reason it is probable that there is some duplication in the lists given here. For instance, there may be no clinical difference between the response to the pituitary estrin and the placental estrin. They act very much alike, to say the least, even though experimentally the former fails to arouse estrus except in normal rats. Further, the physiological opposites of these principles, the antestrous hormone of the anterior pituitary and the luteinizing hormone from the corpora lutea, are so similar in function as to be quite confusing. Then again, it is quite possible for the same thing actually to originate in more than one place.

The most important thing is not these physiological niceties, but the therapeutic application of these laboratory attainments. We are in a better position than ever before to appreciate the claims of some of the clinical writers in past years. The "absurd" and "empirical" suggestions, some of which have been quite harshly criticized, are much more acceptable now since the clinical coincidences of practice have a laboratory background that is hard to deny. Truly "the enigmatic organ" is now explaining many endocrine matters that heretofore have been but dimly understood.

PITUITARY PRODUCTS

Anterior Lobe

ACCRETIN* (1B)—A desiccated concentrate from the anterior pituitary (one part equal to twelve parts of fresh tissue) and thymus which, when fed to immature mice and rats, is capable of causing 100 per cent. increase in the growth rate in from ten to fourteen days as compared with untreated controls from the same litter. Parallel tests indicate that it has a negligible effect on the growth of mature animals. Available in capsules of 5 gr. Dose: As a growth stimulant, 3 or 4 capsules a day for a prolonged period. (X-ray of hand must indicate open epiphyses.)

ANTERIOR PITUITARY (1B)—A defatted desiccation of the anterior pituitary lobes, each part representing five and one-half parts of fresh tissue. Used in hypopituitarism with infantilism, obesity, etc., and experimentally in certain types of bronchial asthma and epilepsy. Dose: From 5 to 30 gr. a day.

ANTUITRIN—An active solution prepared from the total anterior lobe of the pituitary body. Each cubic centimeter contains the equivalent of the soluble extract in 1 Gm. of fresh tissue preserved with chloretone 0.5 per cent. *(Parke, Davis & Co.)*

APESTRIN* (2)—A solution of a potent anterior pituitary estrin capable of causing rut in immature mice and rats. Its effect is upon and through the ovarian mechanism. Used in utero-ovarian hypoplasia, sterility, etc. In fact it is being used in conjunction with Plestrin, or in place of it. Dose: 1 cc. daily or every other day.

APLUTIN*—The luteinizing hormone from the anterior pituitary, similar in action to lutin from the corpora lutea.

PHYONE (2)—The anterior pituitary growth hormone separated by H. B. Van Dyke, of Chicago. As yet of experimental interest only.

PROLAN (1A)—"The antepituitary hormone of Zondek," available in physiologically standardized solution. The smallest amount which in immature rats gives rise to the estrous phenomena is fixed as a "rat unit" (r.u.). By intramuscular injection in infantilism, amenorrhea, and hypopituitarism. Dose: From 100 to 300 r.u. daily. *(Bayer, Meister-Lucius, Leverkusen a. Rh.)*

Posterior Lobe

ELIXIR HYPOPHYSIS CEREB.—An aromatic elixir containing whole pituitary gland, each dram containing the equivalent of ½ gr. of the dried and powdered extract (3 gr. fresh gland). Dose: 1 or 2 fluid drams, t.i.d. *(Squire & Sons, Ltd., London.)*

EXOPHYSIN (1)—A solution of the total extract of the posterior pituitary gland containing "the three separate fractions." *(E. Merck, Darmstadt.)*

GYNOPHYSIN (1A)—The ecbolic hormone or "oxytocin" from the posterior pituitary gland. *(Merck.)*

INFUNDIBULIN (1A) (Infundin)—The first posterior pituitary extract for use in obstetrics, etc. Now called "Infundin." Obtainable in two strengths—"Original Strength," 10 international units per cubic centimeter (equal to standard in U.S.P. X), and half this strength. *(Burroughs Wellcome & Co.)*

LIQUOR PITUITARII (1A)—The U. S. P. name for the physiologically standardized posterior pituitary solution, each cubic centimeter containing the equivalent of 10 international units, as adopted by the Standards Committee of the League of Nations. (The activity of 0.5 mg. of the dry standard acetone-extracted posterior pituitary powder on the isolated uterine muscle of the virgin guinea-pig is defined as one international unit.) Used in labor, intestinal paresis, anuria, and shock as a musculotonic measure. Dose: From 2 to 5 international units intramuscularly *p.r.n.*

OXYTOCIN (1A) (Pitocin)—The uterus-contracting principle from the posterior lobe, standardized to the same oxytocic strength as Pituitrin (Obst.). Used in uterine inertia with hypertension, or in arterial spasm as in eclampsia. *(Parke, Davis & Co.)*

PITUITRIN (1A)—The posterior pituitary extract used as a uterotonic and pressor remedy in uterine inertia, in post-operative ileus with retention of urine, and to prevent or control operative shock. Available in two strengths—"Obstetrical," containing 10 international units per cubic centimeter; and "Surgical," twice this strength. See Liq. Pituitarii. *(Parke, Davis & Co.)*

PITUTHYMIN* (1A)—A stable, isotonic solution of the posterior pituitary oxytocic principle with thymus nucleoprotein, each cubic centimeter containing 10 international units of the former. Used during labor as an ecbolic. It is shown clinically that the combination tends to break up the uterine contractions and prevent spasm. Dose: From ½ to 1 cc. by intramuscular injection, usually once only.

THYMOPHYSIN (1A)—A combination of extracts from the thymus and the posterior pituitary after N. Temesváry. Used in accelerating delivery during the period of dilatation. Administered intragluteally. Dose: 1 cc.; a second or third dose is seldom necessary. *(F. Pezoldt, Vienna.)*

VASOPHYSIN (1A)—The pressor, antidiuretic and intestinal peristalsis promoting principle, or "vasopressin," from the posterior pituitary gland. *(Merck.)*

VASOPRESSIN (1A) (Pitressin)—The blood-pressure-raising and antidiuretic principle of the posterior lobe, standardized to the same pressor activity as Pituitrin (Surg.). Used in operative shock, diabetes insipidus, etc. *(Parke, Davis & Co.)*

19. THE PLACENTA

Galactagogin — Estrin, Œstrin — Plestrin — Plagonin* — Emmenin — Placentin — Placental and Allied Products.*

THE CRITICISM was once made that the source of many endocrine products was offal, for practically all the basic endocrine raw material used to go into the fertilizer tank with other offal. It was evidently the intention of the one making this criticism (in the *British Medical Journal*) to slur the whole subject of organotherapy. Certain it is that the placenta is in the category of offal, yet some startling developments have been made with it, which should change this pessimistic attitude.

Several potent principles have been separated from the placenta and used with decisive advantage in clinical practice. The obvious value of these products far outweighs any criticism of their source, for it is now well known that many a valuable product is obtained from waste material.

For many years it has been believed that the placenta is more than a vascular organ, and it has been suggested that in several respects it acts in an endocrine way. More than thirty years ago it was claimed by M. Letulle and L. N. Larrier, of Paris (*Rev. de gynéc. et de chir. abd.*, 1901, v, p. 195), that certain secreting areas in the placenta were indeed endocrine tissue. The experiments of these workers seemed to be quite conclusive. About the same time a German gynecologist, J. Halban (*Ztschr. f. Geburtsh. u. Gynäk.*, 1903, liii, p. 191), suggested that the chorionic epithelium in the placenta exerts an action on the body somewhat similar to that of the ovaries, and that during ovarian quiescence the placenta undertakes its work to a certain extent. O. O. Fellner, of Vienna (*Arch. f. Gynäk.*, 1913, c, p. 641), showed experimentally that extracts of placenta had a stimulating effect on the growth of the mammæ, uterus, and other genital structures.

GALACTAGOGIN—The galactagogue effect of the placenta, which was sensed by many primitive peoples long before the dawn of scientific medicine, is now much more acceptable from the technical standpoint. This effect is credited to a true hormone, to which the name "galactagogin" has been given. I. Ott and J. C. Scott, of Philadelphia (*Therap. Gaz.*, 1912, xxviii, p. 310), found that the administration of air-dried human placental extract caused increased secretion of milk in a lactating goat, thus confirming the earlier researches of R. Lederer (*Arch. f. d. ges. Physiol.*, 1910, cxxxiv, p. 531). K. Basch, the Hungarian physician, whose report of the physiological developments in the Blazek pygopagous twins (see Chapter 70) caused widespread interest, injected extracts of placenta into adult animals that had

lactated at one time, with the result that a new secretion of milk was produced (*München. med. Wchnschr.*, 1911, lviii, p. 2266). He also tested these extracts on infants in whom the early mammary secretion had ceased, and it was actually renewed. Basch concludes that the so-called "witch's milk" is due to the passage into the fetus of the galactagogue hormone that circulates in the blood of the mother, which, he suggests, comes from the placenta.

The researches of J. E. Lane-Clayton and E. H. Starling, at University College, London (*Proc. Roy. Soc.*, 1905-1906, (B), lxxvii, p. 505), regarding galactogenesis should at least be mentioned here. Some time before their report, however, J. Halban (*Arch. f. Gynäk.*, 1905, lxxv, p. 353) had put forward the view that the chief stimulus to mammary development during pregnancy originates in the placenta. Whether this influence is due directly to a galactagogue hormone or to a subtle overbalancing of other influences that prevent milk production, is not known. However, in the chapter on the placenta in "Endocrinology and Metabolism" (New York, D. Appleton and Company, 1922, Vol. II, p. 661), F. S. Hammett, of Philadelphia, concludes:

"The sum total of the evidence now available justifies the inclusion of the placenta among the endocrine organs. It is to be doubted that the placenta produces a specific secretion concerned in the mammary hyperplasia of pregnancy, and the evidence is cumulatively negative that by any normal secretory process the placenta contributes either to milk secretion or to the etiology of eclampsia. Yet from the data previously recorded and quite recently confirmed by Giesey, that the injection of placental extracts into virgin animals causes a uterine hyperplasia, and from the fact that the rate of growth of breast-fed infants is enhanced when they are subsisting upon milk produced during the maternal ingestion of desiccated placenta, the belief is justified that among the placental functions can be included that of producing a growth-promoting hormone."

Further experiences seem to cast a question on the fact that, administered alone in an experimental way as well as in nursing mothers, placental extract increases the milk secretion directly. Nevertheless it works well in most cases. For instance, a series of cases reported by E. L. Cornell, of Chicago (*Surg., Gynec., and Obst.*, Nov., 1918, xxvii, p. 535), showed that 87 per cent. of the babies whose mothers received desiccated placenta by mouth began to gain by the fourth or fifth day, as against 69 per cent. of those whose mothers did not receive the placental extract. Further, 44 per cent. of the former regained their birth weight before leaving the hospital, as against 24 per cent. of the latter. Hammett (*loc. cit.*) agrees with these findings and concludes that perhaps the placenta may not act as a galactagogue but as a stimulus to the infant's growth. In a large series of cases that he collated, it was shown that there was a smaller postnatal decline, a quicker recovery from the

initial loss, and an increase of 60 per cent. of the initial growth by the thirteenth day in those infants whose mothers had received the placental extract.

The galactagogue action of placental extracts, whether direct or indirect, has been responsible for most of the clinical use of products of this nature. Attention should be called, however, to another remarkable related faculty of placental extract which has to do with its effect on uterine involution. Whether the galactagogue effect indirectly influences the uterus, or whether it is due to the reflex effect of nursing, or whether this influence is direct, is not definitely established. Suffice it to say that the establishment of lactation brings with it the physiological trend of events that assist nature to restore the uterus to its proper size. In many instances placental therapy is as valuable in bringing about uterine involution as it is in establishing or augmenting the supply of milk.

ESTRIN, ŒSTRIN—In connection with the extensive researches into the origin and nature of the female sex hormone, another very interesting development has come about in the last few years. The placenta has been found to be an excellent source of the estrus-producing hormone or estrin. Perhaps this is actually produced by the placenta itself, as is believed by some; or it may be that the placenta serves as a sort of sponge to take up from the blood of the pregnant woman the excess of the female sex hormone, which, during this special period, is more or less superfluous. At least, it has been found that the placenta is very much richer in the female sex hormone than any other tissue, not excluding the ovaries.

This active principle is clearly a hormone. It is possible to demonstrate its activity and measure its potency in quite a remarkable fashion, for the female sex hormone, or estrin, is actually capable of bringing about estrus in ovariectomized animals, and through the researches of E. A. Doisy and his associates in the St. Louis University a method of experimental standardization has been perfected. This test, known as the Doisy test, is considered more fully in the discussion of the female sex hormone (11). By means of the response to this estrus-producing influence, all substances of this nature can be identified and evaluated. As an indirect result, it has been found that this hormone can be separated not only from the follicular fluid (its original source) but from the ovaries (11) and from the urine during pregnancy. Despite the varying sources of these remarkable substances, it appears that they are all one and the same thing. The name "Œstrin" is given to a trade preparation used in England, which is similar to the original placental product of E. C. Dodds, of the Middlesex Hospital.

PLESTRIN*—The placental estrin known as Plestrin was the first of a number of similar substances to be made available. As outlined elsewhere (11), it was substituted for Folliculin in 1927. It is a clear, non-toxic solution containing the estrus-producing substance. It is physiologically standardized in two ways: (1) by the Doisy test on bilaterally ovariectomized rats, and (2) by the trophic test on immature rabbits (see page 96). It has been shown also that this estrin is even capable of rejuvenating senile rats; that is, rut is reestablished in old rats after it has apparently ceased, and they are thus rendered capable of further reproduction. The remarkable trophic effect of Plestrin suggests its use in clinical practice for this same purpose. It has been used chiefly in conditions associated with utero-ovarian hypoplasia, particularly amenorrhea and sterility. Its effect on the circulation and nutrition of the pelvic organs makes it a means of arousing a normal sexual development and activity. Plestrin is given with apparent benefit in cases of delayed puberty and defective development of the secondary sex manifestations, and with excellent success in many cases of endocrine sterility. Several of the nervous and circulatory conditions associated with utero-ovarian hypoplasia, with clinical manifestations including sexual neuroses, frigidity, and minor psychoses such as melancholia, etc., have been quite remarkably modified by a course of Plestrin. The most important indication for this product is endocrine sterility and, as the reader will see (80, 96), there are chances for success in almost 75 per cent. of the indicated cases.

It has been found that Plestrin is best given in the following manner: The average dose, 25 rat units, is injected intramuscularly daily or every other day. Occasionally it is an advantage to double the dose the second month, and in a number of instances 50 rat units, or many times the dosage previously recommended, have been found beneficial. Also, in view of the cyclic character of the utero-ovarian function, the injections may be given in larger amounts or more frequently at or immediately before the expected menstruation or molimen.

Further, in view of the fact that the time during which this substance is likely to be most active is limited and occurs periodically, it is better to give a series of injections each month for at least three or four periods, than the same number of units in regular daily doses for a shorter time.

PLAGONIN*—Because of the recent researches of J. B. Collip at McGill University in Montreal, it is now possible to obtain from this same source still another active principle, which has been called "the anterior-pituitary-like gonad-stimulating hormone from the placenta." This is the alcohol-insoluble fraction, as compared with the alcohol-soluble principle

to be referred to shortly. I have had some success in separating what appears to be a similar substance. This has been called "Plagonin," and it is also known as the maturity-producing hormone. It may be obtained from the blood and urine of pregnancy as well as from the placenta. According to Collip (*Can. Med. Assn. Jour.,* Nov., 1930, xxiii, p. 631), this principle seems to act very much like the anterior pituitary estrin. Its effect appears to be directly on the incretory function of the essential gonad tissue.

Briefly, it is claimed that this hormone liberates the sex hormone by catalysis, and under this influence marked trophic changes are recorded as having been brought about in the essential sex organs. Special emphasis is laid on the negative effect of this substance in castrated animals. In other words, it is entirely different from the other placental principle, Plestrin, which has such a definite estrus-producing and trophic influence in castrated females. Plagonin is active only in the presence of the intact sex glands.

For reasons already outlined, this placental-gonad stimulant is not yet used alone. It has been found advantageous, however, to give it in conjunction with other endocrine stimulants of male gonad function, and since early in 1931 Plagonin has been a part of the formula known as Gonad Co.* (58). Some other possibilities are being developed, but suffice to say that A. D. Campbell and J. B. Collip (*Brit. Med. Jour.,* Dec. 27, 1930, ii, p. 1081) have given their extract subcutaneously in metrorrhagia. They state that "the results in this small group of cases have been most encouraging."

Some research work has been done recently in Germany by E. Philipp, of the University Frauenklinik, Berlin (*Zentralbl. f. Gynäk.,* March 14, 1931, lv, p. 929). By observing the changes in the ovaries of rabbits and mice caused by the implantation of the human placenta of early pregnancy, he has concluded that there is a principle, assumed to originate in the chorionic epithelium, which is believed to be the hormone responsible for initiating the luteinization of the ovary. This induces the production of the corpus luteum hormone, progestin or lutin (11). Production of this substance ceases during the latter months of pregnancy, the corpus luteum of pregnancy undergoes involution, and in consequence there is decidual retrogression. Perhaps this is identical with Zondek's Prolan-*B,* isolated from the pituitary, and with Wiesner's Rho-two.

EMMENIN—There is still another potent principle obtainable from the placenta. It is the fraction announced by B. P. Wiesner, of the University of Edinburgh (*Nature,* March 31, 1929), and perfected in an alcohol-soluble form by J. B. Collip. This is the "ovary-stimulating hormone

of the placenta" for which the name "Emmenin" has been proposed (*Can. Med. Assn. Jour.*, Feb., 1930, xxii, pp. 215, 219; also *ibid.*, June 30, p. 761).

Wiesner, whose preoccupation is not strictly medical (he is connected with the Department of Animal Breeding in Edinburgh), treated fresh placental emulsion or press juice with sulphosalicylic acid and produced an extract that brought about premature maturity in young rats. For example, two injections of the extract, each equivalent to about 5 gr. (0.3 Gm.) of fresh tissue, given a day apart have caused estrus and a coincident uterine hypertrophy by the fifth day! However, the presence of the extracting acid in the product interfered greatly with further developments, and the matter was taken up by Collip at this stage (in September, 1929). Of this product, Collip says (*ibid.*, p. 216):

"It has been found possible to attain great concentration of the active principle. It has been obtained free from protein, salt, lipoid, and œstrin, and in the form of an aqueous solution it may be administered either subcutaneously or orally."

Attention is called to two points mentioned above: (1) the fact that Emmenin is free from estrin or, in other words, *is not the estrin,* and (2) the fact that it is active when given by mouth. Again quoting from Collip's article (*ibid.*, p. 218):

"It has been shown that the same physiological effects may be produced in immature rats by oral administration of the hormone as by subcutaneous injection. The dosage by mouth necessary to produce these effects may not be more than two or three times the effective subcutaneous dose.

"The hormone has been shown to be effective after moderate periods of exposure to the action of the digestive enzymes, pepsin and trypsin."

There is very much more on record about this matter, but there is not space for it here. It must be added, however, that the clinical prospect made clear through this research already is being materialized, and Emmenin and products like it are being used with real benefit. For example, in their preliminary clinical report (*Can. Med. Assn. Jour.*, Feb., 1930, xxii, p. 219), Campbell and Collip relate the control of dysovarism including amenorrhea and dysmenorrhea, as well as an interesting restoration of the endocrine balance in a case of dysovarism with hyperthyroidism. In this case, following suitable doses of this experimental product t.i.d. for a month, the basal metabolic rate was changed from plus 29 to plus 1 and the weight from 119 to 127 pounds. Incidentally, "her nervous symptoms disappeared."

Since this preliminary paper, these same authors have reported a more extended and satisfactory experience with Emmenin (by mouth) in 123 cases of functional ovarian irregularities. (*Brit. Med. Jour.*, Dec. 27, 1930, ii, p. 1080.)

PLACENTIN—Besides all these there is the placental desiccation, the use of which, as the reader will see, is suggested as a means of hastening the immunity in hyperemesis gravidarum. This is based on the principle involved in the immunization response of the organism to certain proteins. This idea, which seems to be original, has been discussed under Vomiting and Nausea of Pregnancy (84). After nearly twelve years of clinical experience, another somewhat similar substance has been prepared in such form that it may be used in my "Placenta Protein Test," a protein sensitization skin test that serves as a means of confirming the fundamental basis of these conclusions, both diagnostic and therapeutic.

PLACENTAL AND ALLIED PRODUCTS

AMNIOTIN (1A)—A suspension of estrus-stimulating extracts from the amniotic liquor of animals. It is standardized by administration to spayed monkeys. Obtainable in vials of 5 cc. containing 100 Allen-Doisy units; also in vaginal pessaries. *(E. R. Squibb & Sons.)*

EMMENIN (2)—An experimental "ovary-stimulating hormone from the placenta," not estrin, recommended by Collip in certain types of ovarian dysfunction.

ESTROGEN (1A)—A solution containing the estrus-producing hormone and certain lipoid substances prepared from "reproductive tissue of pregnant animals" (placenta?). *(Parke, Davis & Co.)*

GALACTAGOGIN (3)—The name given to the hypothetical galactagogue hormone of the placenta.

ŒSTRIN (1A)—A solution of the estrus-producing hormone made from the placenta by the method of E. C. Dodds. *(British Drug Houses Ltd., London.)*

PLACENTIN (1B)—The name given to the comparatively crude placental desiccation that has been in clinical use for the last twenty years. It is a defatted desiccation of shredded beef placenta free from the connective-tissue whorls. Each part represents seven parts of fresh material. Dose: From 5 to 20 gr. three or four times a day.

PLAGONIN* (2)—The gonad-stimulating hormone from the placenta. It is not believed that this product has any therapeutic merit of itself, but, when given in conjunction with the male sex hormone and in cases where the gonads are still functionally capable, it is believed to be clinically active.

PLESTRIN* (1A)—A clear solution of the estrin obtained from beef placenta, each cubic centimeter of which is physiologically standardized to contain 25 rat units. Dose: From 25 to 50 rat units daily or every other day. Recommended chiefly in the treatment of sterility and utero-ovarian hypoplasia.

PROGYNON (1A)—The female sex hormone from the placenta in tablet form for oral administration in utero-ovarian dysfunction, etc. Each tablet contains 30 rat units. Dose: From 1 to 3 tablets daily. *(Schering Corp.)*

PROLAN-B (2)—A placental principle capable of initiating the luteal cycle. Its potency is assayed by noting the changes brought about in the appearance of the corpora lutea of mouse ovaries. (See Prolan—18.)

THEELIN (1A)—A crystalline estrin obtained by Doisy's method from the urine of pregnant women. It may be secured also from the placenta, amniotic liquor, etc. Obtainable only in solution. Each cubic centimeter is standardized to contain 50 Doisy-Allen rat units. *(Parke, Davis & Co.)*

THEELOL (2)—A fraction developed during research with Theelin, which differs from it in that it is six or seven times as active in immature female rats and about one-half as active in adult ovariectomized rats.

20. THE PROSTATE

THERE ARE several points of similarity between the prostate and its product, and the mammæ and the products coming therefrom.

Experimental excision of the prostate, which is not so difficult a procedure, has been performed on dogs in a number of laboratories and the results have been recorded. Unfortunately, prostatectomy is not followed by prompt reactions that could be utilized to evaluate the effects of prostatic extracts.

H. Rohleder, of Berlin (*Deutsch. med. Wchnschr.*, Feb. 17, 1921, xlvii, p. 185), said that medical men and laboratory research workers in general have not considered that the prostate contains an internal secretion, but that it is generally known that there is a humoral relation between the prostate and the testes. Confirmation of this theory is noted in experiments in which prostatic atrophy has followed castration. This atrophy, however, usually is preceded by an effort at hypertrophy, thus indicating a reciprocal or mutual compensatory relationship between the testes and the prostate. Again, with a waning gonad function there is an attempt on the part of the prostate to compensate for this loss; hence it hypertrophies. But, in the case of castration, the connection is completely broken, and the initial prostatic enlargement is soon followed by recession. However, according to Kenneth M. Walker, of London (see *Brit. Med. Jour.*, March 21, 1931, i, p. 482), prostatic atrophy does not occur in castrated dogs if solutions or extracts of the testes are injected. He also states that in the first and second periods of prostatic hypertrophy administration of testicular substance by mouth will give beneficial results in many cases.

Experiments by C. Du Bois and L. Boulet, of Paris (*Compt. rend. Soc. de biol.*, 1913, lxxiv, p. 811), show that fresh aqueous extracts of prostate cause bladder contractions, and that this action is brought about just as well in animals with the cord destroyed as in those in which the nervous system is intact. These experiments were duplicated with similar human extracts.

The experiments with prostatic extracts given orally and parenterally have not been satisfactory to the majority of investigators in this field. Nevertheless, a gradually increasing demand for prostatic extract shows that the empirical use of this product is warranted (85).

PROSTATIC PRODUCTS

PROSTIN (3)—A theoretical, active principle of the secretory cells of the prostate, soluble in water, and exerting a contractile effect on the vesical musculature.

PROSTATE EXTRACT (1B)—A desiccation of the parenchyma of bovine and equine prostate glands; each part equal to seven parts of fresh tissue. Usual dose: From 1½ to 3 gr. three or more times a day, preferably in conjunction with testicular extracts. Solutions are not convenient for clinical use.

21. THE SPLEEN

Lienin, Stagnin, Hormonal — Colloidogénine — Relation of Spleen and Parathyroids—Splenocrin—Spleen Extracts.*

FOR YEARS the functions of the spleen have been under discussion. At one time the spleen was considered to be the graveyard of the red blood-cells. It was also supposed to be a member of the lymphatic system with possibilities of being a generator of leukocytes. An action on intestinal peristalsis as well as on the metabolism of iron has been reported. Still other investigators have demonstrated that the spleen has something to do with the development of immunity and, therefore, may be concerned in the production of the opsonins, precipitins, agglutinins, etc.

In most articles that consider the spleen from the standpoint of its endocrine influences and organotherapeutic possibilities, immunity and resistance to infection are the main points of interest. The spleen is not yet definitely understood; its hormones are not admitted entities; and those who use spleen extracts of various kinds do so under the frown of authority.

Instead of a physiologically standardized spleen hormone, we must be satisfied with the ordinary nucleoprotein solutions and desiccated concentrates. The reader is reminded here that for years the best-known and most acceptable endocrine products, of which the thyroid stands at the head of the list, were no better and no worse than our present spleen extracts.

LIENIN, STAGNIN, HORMONAL—The Germans have used Lienin and Stagnin for years; the French, Colloidogénine and Kinase; and in the English-speaking countries spleen extract of various makes and forms is in moderate demand.

Most of the clinical reports, of which a few are discussed further on (89, 94), are records of the administration of these comparatively crude extracts. First glycerin extracts were used, then desiccations, and later fractional solutions—exactly as was the case with thyroid (24).

It must not be forgotten that Georg Zuelzer's spectacular Hormonal, which was originated in Berlin about 1910, was made from the spleen, and that the effects of this "peristaltic hormone" on the alimentary musculature and conditions—both acute and chronic—are remarkable. Many excellent clinical reports were published, indicating that Hormonal was of life-saving service in maximum degrees of obstipation and intestinal paresis. The only reason that Hormonal and Neohormonal are no longer so widely used is that virtually the same effects can be obtained from other endocrine principles, chiefly the posterior pituitary.

COLLOIDOGENINE—The nutritional influence of spleen therapy, mentioned many times in the literature, is not explained by any specific effect that it possesses. The explanation of Charles Bayle, now of Paris, is original, his conclusions being based on years of patient experimentation on animals while carrying on an extensive consulting practice at Cannes on the Riviera.

Bayle's method is of interest, for he has obtained indubitable results. He prepares an extract of pig's spleen, which is called "Colloidogénine" because he believes that its action is connected with a hypothetical capacity of the spleen to maintain, by means of an internal secretion, the principal mineral elements of the blood in a colloidal state—the so-called "colloidogenic" function. Bayle's theory is this: The blood contains the mineral elements in two forms: (1) those in a colloid state suitable for cellular appropriation, and thus not suited for elimination by the kidneys; and (2) the mineral cellular wastes, which are dissolved in the plasma and destined for elimination. If these elements lose their colloidal form, they are promptly eliminated, and a condition of demineralization obtains. The capacity to maintain the mineral salts in a colloidal state is evidently of considerable importance, and, according to Bayle, its regulation seems to belong to the spleen.

RELATION OF SPLEEN AND PARATHYROIDS—The relation that experimental spleen therapy (and its clinical use also) bears to the mineral metabolism has shown that it has several features in common with the parathyroid hormone, which exerts a well-known influence on calcium fixation.

In my laboratory some years ago, Horace A. Hall and E. Ablahadian (*California and West. Med.,* March, 1925, xxiii, p. 289) showed that spleen extract exerts an effect on the blood calcium similar to that of parathyroid. More recently, J. C. Brougher, of Vancouver, Washington, has confirmed this similarity of action and has shown that there is an apparent synergism between the spleen and the parathyroids. Removal of the spleen from dogs was followed by hypocalcemia. When a desiccated spleen extract was fed to these splenectomized dogs, the low calcium index was promptly raised to normal, although identical treatment to parathyroidectomized dogs had no such effect on the calcium figure. A third group of parathyroidectomized dogs were then splenectomized with a resultant further loss of lime. Quoting from the *Journal of the American Medical Association* (Sept. 27, 1930, xcv, p. 937):

"From the studies here discussed it appears that the spleen is likewise concerned in calcium metabolism. Furthermore, it appears that the results might even be interpreted to mean that, in the absence of the parathyroid glands, the spleen can take over their function of preventing tetany. These intricate relationships between organ systems illustrate the ends to which

the organism as a whole will go in order to preserve the vital equilibrium; furthermore they indicate, in some measure, the inherent difficulties in outlining effective therapy."

This is especially encouraging to me because for years I have urged the use of spleen to supplement parathyroid therapy where indicated, and of parathyroid to enhance the value of spleen extract. It also seems to confirm Bayle's ideas about mineral fixation or colloidogenesis, and may be the best of the several explanations of the *raison d'être* for splenic organotherapy.

SPLENOCRIN*—For the foregoing clinical and experimental purposes, the usual extracts, both soluble and desiccated, have been used. More recently it seemed advisable to deproteinize still further the solutions in use, as the work of von Zumbusch with massive injections of spleen solution for the treatment of certain dermatoses and other conditions associated with eosinophilia called for doses that frequently caused protein reactions. The solution known as Splenocrin was changed, therefore, by the precipitation and removal of a further proportion of protein, with the result that the present product contains only 40 mg. per cubic centimeter of splenic solids. It is sometimes most helpful in urticaria (50).

SPLEEN EXTRACTS

COLLOIDOGENINE (1B)—An extract of spleen used as a means of augmenting the mineral metabolism and recommended chiefly in tuberculosis by Charles Bayle. Obtainable in ampules (dose 5 cc. daily in series), syrup (each tablespoonful representing 25 Gm. of fresh spleen), and powder in cachets. *(Lab. Chaix, Paris.)*

HORMONAL (1)—The peristaltic hormone prepared from beef spleen by G. Zuelzer, in solution with 0.4 per cent. tricresol. Available in solution for intramuscular or intravenous injection in the treatment of obstipation, alimentary paresis, especially acute paretic conditions. Dose: 20 cc. *(Schering-Kahlbaum A.-G., Berlin.)*

LIENIN (1)—A desiccated extract of hog spleen for oral administration. One part equals five parts of fresh pulp. In powder or tablets. Dose: 10 gr. or more t.i.d. *(E. Merck, Darmstadt.)*

MOTILINE (3)—An enterokinetic principle separated by L. Hallion and E. Enriquez, of Paris, from intestinal extracts and claimed by them to be identical with Hormonal *(q.v.)*.

NEOHORMONAL (1)—A perfection of the original solution of Hormonal (Zuelzer) from which all albuminous substances are removed. *(Schering-Kahlbaum, Berlin.)*

SPLEEN EXTRACT (1B)—A desiccated defatted extract, usually of beef spleens. Each part equals five and one-half parts of fresh pulp. Dose: 5 gr. or more *p.r.n.*

SPLENOCRIN* (1)—An active fraction from the spleen (1:37) containing a principle with an influence on the mineral balance and nutrition of the skin. This product is not physiologically standardized. Used in certain asthmas and dermatoses accompanied by eosinophilia. Dose: From 2 to 20 cc. by intramuscular injection.

STAGNIN (1B)—A hemostatic remedy obtained by autolysis of horse spleen. It is a yellowish-brown powder, soluble in water. Applicable in gynecology, especially in uterine bleeding. Administered intramuscularly. *(Schering-Kahlbaum, Berlin.)*

VASODILATIN (3)—A hypothetical depressor substance presumed by its sponsor, L. Popielski, to be present in extracts of spleen and other tissues. It is not histamine, but it is difficult to produce it entirely free from histamine.

22. THE STOMACH

Gastron—Gastrin—Myogestin—Ventriculin—Stomach Preparations.*

FOR MANY years, stomach lining has been used as a source of the enzyme, pepsin, which is employed extensively in medicine and manufacture as a digestant of protein.

GASTRON—Thirty years ago, the famous Paris internist, A. Gilbert, expressed a preference for a powdered extract of gastric mucosa rather than pepsin or natural gastric juice, which at that time was in therapeutic vogue as a result of the work and claims of Pavlov and his associates in St. Petersburg. Gastric extract is still used by some gastro-enterologists, and an excellent "total" preparation, known as Gastron, is quite generally available.

It will be seen shortly, however, that, in this very source, there lay a means of accomplishing results of an entirely different nature; and, until the recent discovery of these new potentialities, gastric extract has not been used very extensively.

GASTRIN—Soon after the reports about secretin began to appear (10), it occurred to several workers to look for an analogous hormone in the gastric mucosa. In 1909, J. S. Edkins, of Liverpool, secured an active substance from the gastric walls near the pylorus, calling it "gastric secretin." Later it was named "gastrin." Referring to the results of this work, the editor of the *Journal of the American Medical Association* (1913, lx, p. 305) says:

"Edkins has carried out experiments to see whether such a chemical mechanism, in distinction from the nervous control that is usually called on to elucidate the phenomena of secretion, may not also serve to explain the secretion of the gastric juice when food is introduced into the stomach. He finds that substances such as peptones, broths, dextrin, etc., which are known to induce gastric secretion when ingested, are without influence on the secretory act if they are injected directly into the blood stream; but, when such known excitants of secretion are allowed to stay with the pyloric mucous membrane, and a decoction of this is then injected into the circulation, a secretion of both acid and peptic enzyme into the stomach ensues. Infusions of the cardiac portion of the stomach or of other organs do not act in this secretion-producing manner. Edkins concludes that this typical secretion of gastric juice is determined by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane, in which they produce a substance which, entering the blood stream, is carried to the gland-cells of the stomach where it acts as a specific excitant of their secretory activity; this is the gastric hormone—'gastric secretin.' "

The chief characteristic of a hormone consists in correlating the activities of the body, the product of one organ inducing activity of another more or less remote from it. It has been noted by C. D. Aaron, of Detroit (*Jour. Am. Med. Assn.*, 1912, lviii, p. 407), that

"it is an essential peculiarity of most hormones that they act on other organs of the body, whereas the hormones of the gastro-intestinal tract have no influence on the general system. The hormones of the digestive apparatus act on the digestive secretion."

It will be clear, then, that the principal usefulness of hormone-bearing extracts of the various parts of the digestive tract will be confined to their influence on the digestive activities; and their capacity in this direction deserves to be studied more extensively and applied more frequently in clinical practice.

Little clinical use has been made of this information largely because secretin takes the place of gastrin, and, too, because hydrochloric acid arouses the production of both.

MYOGESTIN*—For some time, parallel work has been done by W. B. Castle, at Harvard University, and C. C. Sturgis, at the University of Michigan, who attempted to elucidate some of the problems connecting the gastro-intestinal symptoms in patients having pernicious anemia with their abnormal blood production.

Of course, it has been known for many years that achlorhydria and achylia gastrica are virtually pathognomonic of pernicious anemia, and it has been found that the gastric aspects of many of these patients are in direct relation to the blood findings and also to the remissions.

Because achlorhydria is the rule in true pernicious anemia, it has been presumed that the gastric insufficiency is a connecting link in the vicious circle of symptoms from which these patients suffer. In other words, the lack of acid in the stomach prevents certain normal digestive developments that not only are necessary to the proper digestion and assimilation of food, but that have to do with the physiological events connected with hematopoiesis.

In 1929, Castle (*Am. Jour. Med. Sc.*, Dec., 1929, clxxviii, p. 748) reported that he had experimented on several cases of pernicious anemia with prominent digestive symptoms. Healthy persons would eat a certain amount of beefsteak and then permit it to be removed from the stomach after varying lengths of time (usually from forty-five minutes to an hour) so that it could be given to these anemic patients. This artificial digestive service brought about not only nutritional improvement, but also marked

and prolonged remissions in the blood-picture. For example, eight of ten patients showed marked clinical improvement within a week. Characteristic increases in the reticulocyte counts were noted, and improvement was progressive. In three cases, the red blood-count showed a gain of 2,000,000 within two weeks! As Castle says, the response occurring in eight of the ten patients treated with the regurgitated material "was entirely comparable with what might have been expected with moderate uniform daily doses of liver." This interesting report is concluded with the following statement:

"In contrast to the conditions within the stomach of the pernicious anemia patient, there is found within the normal stomach during the digestion of beef muscle some substance capable of promptly and markedly relieving the anemia of these patients."

Just how this influence is brought about is not yet fully established, but two conclusions are reached by Castle and W. C. Townsend, of Boston, in one of their articles on the relationship of achylia gastrica to pernicious anemia (*ibid.*, p. 764):

"It is believed that the correlation between the production of an effective substance and the presence of a normal proteolytically active gastric juice in contrast to the demonstrable lack of both in the patient with pernicious anemia, adds strength to the validity of the original hypothesis of the particular nature of the disease.

"It is believed that for the first time a relationship between the stomach and the function of the bone-marrow of the human being has been demonstrated; and the general belief that the integrity of the stomach is unnecessary to proper body metabolism brought into question."

More recently, Castle, C. W. Heath, M. B. Strauss, and W. C. Townsend (*Jour. Am. Med. Assn.*, Sept. 26, 1931, xcvii, p. 904) confirm their previously expressed suspicions and make the following assertion with apparent confidence:

"It therefore appears that the chain of evidence is complete for the substantiation of the original hypothesis under which this work was begun: namely, that pernicious anemia is a deficiency disease resulting not from a direct inadequacy of the diet but from a conditioned deficiency produced by the failure of some function of the normal stomach to take place in the stomach of the patient with pernicious anemia."

These reports are almost as startling as those that were published some time before regarding liver feeding in this same disease, and once again the value of oral organotherapy is emphasized. However, when a method like this comes to be translated into every-day practice, the elements of convenience and esthetics offer certain barriers that are almost insurmountable. The expense of arranging for "an associate digester" and the nastiness of eating

something that has just been taken from another person's stomach, certainly militate against the wide-spread use of such a measure.

On general principles it seemed to me that the digestion might just as well be done artificially in vitro, thus bringing about essentially the same changes in the meat. This idea has been materialized, and from a clinical standpoint the product, Myogestin,* is found to be definitely active. However, in order that the conditions might more nearly approximate those in the stomach, the digestion is not done with the isolated ferment, pepsin. Instead, a suitable proportion of an emulsion of fresh stomach is digested with beef muscle in liquid form, with hydrochloric acid to make the acid concentration 0.3 per cent. After digestion the mixture is centrifuged and the filtrate brought to dryness. (The solid débris is discarded.)

The reasonableness of this idea has been confirmed by the conclusions of others. In a paper read at Ann Arbor, Michigan, on March 21, 1930, C. C. Sturgis (reference not found) stated that 200 Gm. of beefsteak, fed daily to a patient with pernicious anemia, has no effect on the disease. However, if the beef muscle is first fed to a healthy man and then, after it is partially digested, removed from his stomach and fed to the pernicious anemia patient, a remission is induced. Similar results are obtained if the beef muscle is digested in vitro with normal gastric juice. Just as the stomach of the patient with pernicious anemia is unable to secrete hydrochloric acid, it is unable to liberate from beef muscle this substance that will benefit the disease. It is postulated by Sturgis that there is some new enzyme (probably not pepsin) in normal gastric juice which is responsible for the effect.

Shortly afterward, James S. McLester, of Birmingham, Alabama (*Bull. Chicago Med. Soc.*, May 10, 1930, xxxii, p. 26), in his paper, "The Clinical Relations of Achlorhydria," gave support to the opinions of the Michigan workers, and it is safe to predict that before long there will be a number of clinical papers confirming this interesting development.

Thus we are led to the discovery of an apparently new remedy for use in patients with pernicious anemia. It consists of soluble extract of beef muscle that has been digested by contact with an emulsion of fresh stomach and hydrochloric acid.

So far as I know, Myogestin is apparently a new and original product. There is no record in the literature of anything like it. Not only is it a food (for it is a solution of the predigested, defatted, muscle proteins), which is very easily assimilated, but there evidently is present in it a subtle but unknown factor that sets in motion the train of circumstances that appear to be so helpful to these patients. What this particular substance is,

still remains to be determined. It is not even known whether it is an enzyme or a hormone; but, until it is possible to isolate it and make it available as a separate entity, we shall be satisfied to give this preparation for the dual purpose of increasing the nutrition of pernicious anemia patients and of contributing to the organism a substance that Nature apparently is unable to supply. Incidentally, its value is not limited to the treatment of pernicious anemia; it is recommended also in all forms of achylia and achlorhydria.

VENTRICULIN—As a result of extended research in the Simpson Memorial Institute at Ann Arbor, Michigan, it was discovered by R. Isaacs and C. C. Sturgis that an active hemopoietic could be prepared from stomach tissue—*not* scrapings.

This new remedy was first used in the University of Michigan and found to be capable of bringing about remissions in pernicious anemia in a somewhat similar manner and degree to liver extract or hemopoietin (13).

The process as outlined by these writers (*Jour. Am. Med. Assn.*, Aug. 23, 1930, xcv, p. 585) follows:

"The stomachs of hogs are collected, the gross fat and mesentery are removed mechanically, and the material is chopped very fine. It is not necessary for the organs to be used immediately, and the blood-maturing activity is not lost even if the material is from twelve to eighteen hours old before desiccation is begun. It is believed that a secretion of the mucosa, possibly of the nature of an unnamed enzyme, acts on the muscle layer when the two are ground together. Either layer alone appears to possess very little potency when fed to patients with pernicious anemia. After desiccation, the fat is removed with petroleum benzin. The resulting material is a dry granular powder, which swells in water but does not dissolve. About 14 to 15 Gm. of the dried material represents 100 Gm. of fresh stomach. A complete remission has been instituted in a patient with pernicious anemia with 15 Gm. of this material daily, but the dosage that is clinically most effective is 10 Gm. of the powder for each million deficit in the red blood-cell count. The maintenance dose is 10 Gm. from five to seven times a week when the red-cell count reaches from 4,500,000 to 5,000,000 per cubic millimeter. The 10-Gm. dosage represents some margin of safety, as effective remissions have been maintained with 7 Gm. daily. The dried stomach may be taken in water or tomato juice, either as a thick purée or in suspension. It may be taken with or between meals."

There is a growing literature on the subject, especially in Germany, where this idea has been taken up with avidity.

The antianemic influence of desiccated whole hog stomach in the pernicious type of anemia is summarized by A. B. Brower and W. M. Simpson, of Dayton, Ohio (*Am. Jour. Med. Sc.*, Sept., 1931, clxxxii, p. 319), as follows:

"1. Desiccated defatted whole hog stomach in adequate dosage is effective in producing a prompt and continued remission in cases of pernicious anemia.

"2. Occasional patients with pernicious anemia who do not respond completely to liver or its extract will obtain a more satisfactory response with stomach therapy.

"3. The administration of dilute hydrochloric acid is apparently unnecessary in conjunction with stomach therapy. The advent of liver and stomach therapy appears to have eliminated the necessity for repeated transfusions in the treatment of pernicious anemia. . . .

"6. Mild neurologic symptoms disappeared or were distinctly alleviated in the eight patients who experienced such symptoms prior to the institution of stomach therapy."

STOMACH PREPARATIONS

EXO-GASTRINE (1B)—An extraction by "exolysis" of a glycerinated maceration of scrapings of hogs' stomachs. Used as a substitute for natural animal gastric juice as well as for the commonly used pepsin-HCl mixture. *(Laboratoires Byla, Paris.)*

GASTRIN (2)—An experimental acid extract of scrapings of the pyloric walls containing a secretin-like principle.

GASTRON (1B)—A soluble extract of entire stomach in an acid-aqueous-glycerin menstruum. For use in digestive disorders and malnutrition. Dose: From 2 to 4 teaspoonfuls at meals. *(Fairchild Bros. and Foster.)*

MYOGESTIN* (2)—A digest of fresh beef muscle with an emulsion of entire stomach for use in achylia gastrica, especially in conjunction with pernicious anemia. After centrifugation, the solid material is discarded and the liquor brought to dryness. This is a soluble protein food, containing what has been called "a new hormone." Available in vials of 4.5 Gm. Dose: The contents of one vial twice daily.

STOMOPSON—A desiccated extract of stomach in powdered form for use in the treatment of the anemias. Dose: From 2 to 3 teaspoonfuls three or four times a day. *(Promonta, Hamburg.)*

VENTRICULIN (1B)—A granular desiccation of hogs' stomach in vials containing 10 Gm., each representing the equivalent of 65 Gm. of the entire gastric walls, defatted; also in 100-Gm. bottles. The hematinic dose is from 10 to 20 Gm. daily. *(Parke, Davis & Co.)*

23. THE THYMUS

Thymin—Thymocrin—Karkinolysin—Thymus Products.*

THE THYMUS is a glandular oddity—lymphatic in structure, epithelial in origin, and very distinctly endocrine in its relations. It is a small, irregular pad of lymphoid tissue lying beneath the upper part of the sternum. Despite the facts that the thymus plays a decided part in the early endocrine balance, and that potent extracts have been made from it which are doubtless experimentally active and of some therapeutic value, as yet virtually no leading endocrinologist will admit that this gland is an endocrine organ. In this connection, Walter Timme, of New York, whose name is associated with an important thymus syndrome (93), says in his article in Cecil's "Text-Book of Medicine" (Philadelphia, W. B. Saunders Company, 1930, p. 1192):

"Although there is little or no experimental basis for the assumption that the thymus is an incretory gland, clinicians persist in associating several very interesting [endocrine] syndromes with irregularities in its activity."

The thymus is an organ of infancy, proportionately larger at birth than at any other time, although when its involution begins it is somewhat larger than previously. At this time the lymphoid elements in the gland normally begin to fade away, until by six or seven years the thymus is a negligible "rest," essentially epithelial in character. This may be "resurrected," however, in certain cases of hyperthyroidism, as we shall see later (63). It is these epithelial cells that hold "the mystery of the adult thymus."

Because of circumstances, the physiology of the thymus has had to be studied largely in connection with its abnormalities, and this is apparently one of the reasons why there is still so much difference of opinion about the fundamentals.

THYMIN — Experimental proof of convincing accuracy shows that the thymus is, in its period of activity at least, an essential organ; and, while thymectomy is not always fatal, every case thus treated manifests well-defined symptoms, some of which can be modified by thymus organotherapy. For this purpose, extracts, both soluble and desiccated, which are presumed to contain the hypothetical hormone, thymin, have been made in various countries.

A. E. Lampé, of Halle, gives a very interesting presentation of this subject, from both the anatomical and the physiological view-point. The experiments of various investigators are reported, and the results are summarized (*Am. Jour. Obst.*, 1913, lxvii, p. 808) as follows:

The thymus gland is an organ of vital importance, as extirpation at the height of its development results finally in death. Probably its most important function consists in the inhibition of acids and the consequent removal of injurious substances from the blood. The function of the supposed active principle gives an explanation of the disturbances occurring in the calcium metabolism after extirpation of the organ, as well as of the changes in bone and in the central nervous system. Complex relations exist between the thymus and the various organs of internal secretion. This is especially true of the spleen, for it is believed that this organ is "prepared" by the thymus to take up some of the still unexplained functions of the thymus after its involution.

Let us now see what happens to dogs when the thymus is destroyed by X-ray or removed, for the dog shows the most striking characteristic changes. According to H. Klose, the weight of a thymectomized dog rises normally for the first two or three months, but the general habitus differs strikingly from that of the healthy controls. Quoting from the review by A. M. Pappenheimer, of New York (*Am. Med.*, April, 1914, ix, p. 212):

"The muscles are flabby, the animals are pasty and bloated, fatigue easily, sweat rapidly, breathe hard with faint exertion, and become sedentary in their habits. The gait is awkward, and the bones bend under the weight of the body, so that the dogs have a clumsy, squat appearance. The appetite is increased, and the animals eat voraciously and without discrimination."

These symptoms continue into the second or third month, when the weight begins to decrease and the weakness, especially of the bones, increases. This author continues:

"Growth is arrested, the animals are dwarfed and do not attain sexual maturity. In spite of the loss of weight, the appetite continues extreme. Eventually, the dogs are hardly able to walk, but rest for most of the time sitting on their hind legs. Often they exhibit a coarse tremor, and their galvanic excitability is increased, just as in experimental tetany, but not to the same degree. Mental deterioration sets in, and the dogs no longer recognize their master, and eat all sorts of objects indiscriminately. This illness, with periods of improvement, lasts from three to six months, or rarely to the fourteenth month. The dog in this period is subject to intercurrent infections which often end fatally. . . .

"The pathological changes, aside from the extreme inanition, are most striking in the bones, although alterations, possibly secondary to the general nutritional disturbance, are described also in the central nervous system. The essential change in the bones appears to be a defective calcification associated with increased resorption. . . . The essential fact that the thymus exercises an important influence upon the proper development of the skeleton, seems to be definitely established."

Obviously, the clinical conclusions regarding the part that the thymus principle plays in the growth and development have been based on abnormal rather than normal function, and we are now convinced that endocrine abnormalities cause prompt compensatory or cooperative reactions on the part of other associated organs. Hence our intimate knowledge of thymus function can never be accurate.

For example, it is known that in children with an enlarged thymus there is a strange nutritional upset that predisposes to attacks of cyanosis, which end in the dread mors thymica (93). Is this picture of *status thymicolymphaticus* a purely thymic disorder, and are the other endocrines normal? The answer is in the negative, hence we are handicapped in making accurate deductions.

The most plausible theory is that outlined by Walter Timme (*New York Med. Jour.*, July 6, 1921, cxiv, p. 12):

> The hypoplastic state associated with persistent or enlarged thymus, a *status thymicolymphaticus,* arouses a compensatory reaction in order to overcome the hypoplastic tendency. The low blood-pressure, hypocalcemia, and hypoplastic blood-vessels, with the inevitable asthenic syndrome, cause serious adrenal stress. Besides this, the enlarged thymus itself causes pressure on the vagus and the sympathetic plexuses at the base of the heart, upsetting the automatic control that enables the cardiovascular mechanism to meet emergencies. This increased pressure on the vagus of itself may stop the heart. The adrenal mechanism, continually stressed to the limit, finally fails in the emergency, and the patient dies suddenly.
>
> The patients who adjust themselves to these circumstances are those who have enough adrenal reserve and capacity to enlarge these structures to meet the demands on them. As a result of this increased cortex activity we find an early puberty with abnormal maturity (see page 435).

Again, the thymus plays a rôle in growth regulation. As H. Klose and H. Vogt have shown by their thymectomy experiments ("Klinik und Biologie der Thymusdrüse," Tübingen, Verlag der H. Laupp'schen Buchhandlung, 1910), thymectomy causes the bones to soften and bend. There is also a serious derangement of nutrition, developing ultimately into a fatal cachectic state. Other researches show that, by feeding these animals extracts containing thymin, or by preparing nucleoprotein thymus extracts and injecting them into these animals, the defects may be prevented or mitigated, depending upon the extent of the upset, the amount of the extract, and the length of the treatment. Is this not exactly parallel with the results from similar excision experiments and replacement therapy with the thyroid, the adrenals, or the parathyroids?

An active growth-stimulating influence has been reported from both experimental and clinical thymus feeding. The conclusions of J. H. Hammar, the Swedish anatomist, of Upsala, and of H. Klose (already outlined) suggest this. This growth principle is still little understood, its effect not having been acceptably explained. It has been suggested variously that (1) it is a direct catalyst to bone growth, (2) it cooperates with the parathyroids and perhaps the spleen in making lime acceptable to the organism, (3) it balances the gonads, "keeping them under" until growth is arranged for, and (4) it arouses both the thyroid and the anterior pituitary in their growth-regulating influences. Thymus feeding facilitates growth, especially when it is combined with the anterior pituitary growth hormone as in the product known as Accretin* (18).

THYMOCRIN*—In 1926 a total thymus extract was prepared for F. F. Ward, of New York City, who was seeking a means of controlling psoriasis. Several products were made, and, after a few experimental rebuffs and interesting clinical experiences, Ward reported success in his work. This product was made available in 1928 under the name "Thymocrin." There is some clinical information on this matter in Chapter 50.

KARKINOLYSIN—Since 1929 Adolph M. Hanson, of Faribault, Minnesota, whose "parathyroid-hydrochloric X" in 1922-1923 turned out to be the first standardized parathyroid hormone, has been working on cancer and concentrating especially on the influence of certain extracts from the thymus (*Minnesota Med.*, Jan., 1930, xiii, p. 17; also Feb., 1930, xiii, p. 65). Hanson's work with thymus has been based on the theory that epithelial neoplasms result from the loss of the natural cellular influence that maintains the normal mitosis or cell division. He says:

"With the idea that the internal secretion of the true thymus is locked up in the giant epithelial cells, and on the supposition that this thymic internal secretion preserves normal epithelial health throughout the entire body, *i.e.*, that it controls and keeps up normal epithelial growth and cell repair, I set myself the task of isolating the true thymic hormone. In order to do this it seemed that a method of extraction that would break down the gland completely and that would exclude the lymphoid elements held out the best hope of solution."

The Hanson extract, known as "karkinolysin" (because it appears to exert a lytic effect in certain malignant tumors), is apparently quite similar to the Thymocrin mentioned above. At least, the latter also is free from histone nucleate (see *Minnesota Med.*, Jan., 1930) and gives no precipitate with acetic acid—two points to which Hanson has called attention that differen-

tiate his solution from soluble thymus extracts and nucleoproteins, with which he has been able to compare his lytic solution.

Early experience with karkinolysin indicates that it is capable of exerting a very definite and selective action in the epithelial types of cancer, *i.e.*, carcinoma. It is given by daily intramuscular injections for several months in highly malignant types, yet in the cancers of slower growth he has given as few as twenty injections.

It is interesting to note that there are several connecting links between the thymus and the adrenal cortex. In the latter, one finds cells quite similar histologically to the epithelial cells in the thymus, since the cells in the fascicular and reticular layers are stained with eosin. The paper on "The Bovine Thymus," by A. M. Hanson (*Minnesota Med.*, Jan., 1930, xiii, p. 17), contains evidence that satisfactorily differentiates the neck and heart thymus of cattle, and shows that thymus aplasia is not complete, as once was the accepted opinion, but that "the epithelial thymus" persists. It contains some data that have not yet received the attention they deserve.

THYMUS PRODUCTS

THYMIN (3)—A hypothetical thymus hormone, or the active agent in thymus extracts.

THYMIN (1B)—A German extract of calves' thymus, evidently a total desiccation. Put up in tablets of 0.5 Gm. Dose: 2 or more tablets *p.r.n.* *(v. Poehl & Söhne, Berlin.)*

THYMOCRIN* (1B)—A solution from the neck thymus of calves, each cubic centimeter equal to 42 gr. of fresh tissue and containing 50 mg. of solids. Used chiefly in the treatment of psoriasis. Dose: 1 cc. daily or every other day by intramuscular injection.

THYMUS EXTRACT (1B)—Desiccated defatted calves' thymus in tablets or capsules. Each part equal to seven parts of fresh material. Dose: From 10 to 30 gr. t.i.d.

24. THE THYROID

Iodothyrin—Thyroglobulin—Thyroxin—Clinical Comparisons—Standardization—Administration—Thyroid and Antithyroid Products.

THE MEDICINAL use of thyroid is stated to have been known for many centuries. In the early nineties, George R. Murray, of Newcastle, England, advised his patients to get fresh thyroid glands from their butchers and to eat them in sandwiches. The first pharmaceutical products were in glycerin. The first tablets of desiccated thyroid substance were offered in this country in 1893 by Parke, Davis & Company.

IODOTHYRIN—Beneficial results from this medication led to a lively interest in the functions and composition of the thyroid. Although not the first to suspect the presence of iodine in the thyroid, it remained for E. Baumann, a German physiological chemist, to publish in 1895 his accidental discovery that iodine is a component of the normal thyroid gland (*Ztschr. f. physiol. Chem.*, 1895, xxi, p. 319). By boiling sheep's thyroids with 10 per cent. sulphuric acid for several hours, an insoluble, reddish mass was separated which, on further purification, proved to be a substance containing 9.3 per cent. iodine, which he named "iodothyrin" (thyroiodin). This substance was believed to be the active principle of the thyroid. It had the same physiological action as thyroid in a qualitative way, but not quantitatively, as has since been shown by numerous investigators—*e.g.*, F. C. Koch, of Chicago (*Jour. Biol. Chem.*, 1913, xiv, p. 101). Many preparations are only slightly active while others show as high as 75 per cent. activity by the different tests. The German "thyroidin" probably is a preparation of iodothyrin.

THYROGLOBULIN—At the time attention was directed so strongly to the iodine compounds in the thyroid, many concerned themselves with the chemistry of the thyroid protein. In 1899 A. Oswald, of Zurich (*Ztschr. f. physiol. Chem.*, 1899, xxvii, p. 14), separated globulin by half saturation of a saline extract of thyroids with ammonium sulphate. This protein he named "iodothyroglobulin." Its physiological action has been demonstrated to be equal to that of thyroid of equal iodine content. Iodothyrin can be separated from it.

It has been shown by Ludwig Hektoen and other Chicago workers that thyroglobulin is the essential thyroid secretion, and experiments by these men show that its presence can be demonstrated quite easily in the venous blood and the lymph coming from the gland (*Proc. Nat. Acad. Sc.*, 1925, xi, p. 48).

These two substances, iodothyrin and thyroglobulin, are the two most significant products obtained in the early history of the study of the thyroid. However, there were others of passing interest, including S. Fränkel's thyro-antitoxin (*München. med. Wchnschr.,* 1896, xliii, p. 476), an extract nearly free from protein and of doubtful thyroid activity. Thyroglandol is another such preparation obtained by perfusion of the thyroid. The resultant extract was believed by Asher to be physiologically active, but possibly his test methods were faulty.

THYROXIN — For fifteen years following the preparation of iodothyroglobulin no outstanding discoveries in the field of thyroid chemistry were made. On December 25, 1914, E. C. Kendall, of the Mayo Clinic, obtained the first pure crystals of his acid-insoluble *A*-iodine compound, later called "thyroxin" (*Jour. Am. Med. Assn.,* 1915, lxiv, p. 2042). It was obtained by hydrolysis of thyroid substance with 5 per cent. sodium hydroxide solution, precipitation of the *A*-iodine compound with acid, subsequent treatment with barium hydroxide, and crystallization from acid alcohol. This white crystalline compound contained about 60 per cent. iodine and was capable of causing symptoms of hyperthyroidism when injected into man or dogs.

The acid-soluble constituents of the thyroid, *B,* produce "no apparent effect when given to normal dog or man, but certain symptoms of myxedema and some conditions of the skin appear to be relieved by the administration of *B* alone." Itching of the skin, soreness of the joints, muscular cramps, and dermatitis exfoliativa, all symptoms not infrequently found in myxedema, could be relieved by this *B* fraction (*Endocrinology,* April, 1917, i, p. 153).

At the meeting of the Association for the Study of Internal Secretions in Chicago, June, 1918, Kendall announced the selection of the name "thyroxyindole" for his *A*-iodine compound as a result of his study of the chemical nature of the substance and his belief that it was a derivative of oxyindol. The name was changed by him to "thyroxin" (*Endocrinology,* April-June, 1918, ii, p. 81) after it was proved that his original ideas of the chemical structure were erroneous, and that thyroxin is not an indol derivative.

One milligram of thyroxin given to an adult causes an increase in the rate of combustion of approximately 2.5 per cent. It causes a drop in blood-pressure and an increase in pulse rate, respiration, and metabolic rate. It apparently acts as a catalyst, though J. A. Dye and R. A. Waggener, of Cornell University (*Am. Jour. Physiol.,* June, 1928, lxxxv, p. 365), present evidence that this substance is not catalytic, since the action of thyroxin is too delayed, and that it acts on the intracellular oxidizing system.

By the spring of 1917, a total of 7 Gm. of thyroxin had been prepared by Kendall at an expense of more than $350 a gram (E. C. Kendall, "Thyroxin," New York, Chemical Catalog Company, Inc., 1929, p. 24). Because of this heavy cost, C. R. Harington, of University College, London, set about to increase the yield, and in 1926 (*Biochem. Jour.*, March-April, 1926, xx, p. 293) described the isolation of crystalline thyroxin in a yield of 0.12 per cent. of the dried gland, approximately ten times Kendall's yield. This increased yield may have been due more to a richer source of thyroxin in English glands than to the variation of the method of preparation, since Kendall (*ibid.*, p. 40) has been able to isolate five times as much thyroxin from hog thyroids in July as in January. It must be added here that many samples of desiccated thyroid of known therapeutic potency do not yield crystalline thyroxin.

At that time Harington, with G. Barger, presented proof that thyroxin is a tetra-iodo derivative of the *p*-hydroxyphenyl ether of tyrosine but was unable to state the position of the four iodine atoms until the following year (*Biochem. Jour.*, Jan.-Feb., 1927, xxi, p. 169) when he synthesized a substance identical in every chemical and physiological way with the natural product. It is tetra-iodo-oxyphenyl tyrosine and has the empirical formula of $C_{15}H_{11}O_4NI_4$.

According to Kendall (*Ann. Clin. Med.*, Jan., 1923, i, p. 256), the average amount of thyroxin required daily is about 1/120 gr. of the pure crystals given intravenously. Apparently from 14 to 15 mg. of thyroxin is functionally available in the body constantly.

The structural formula of thyroxin shows that it has one asymmetric carbon atom, a fact which suggested that it should be optically active. Due to the drastic alkali treatment, the natural product is as inactive as the synthetic product, since a racemic mixture of the dextro- and lævo- forms results. In 1928 Harington (*Biochem. Jour.*, Nov.-Dec., 1928, xxii, p. 1429) prepared lævo-thyroxin and showed it to be about three times as effective on the oxygen consumption of rats as the dextro- type, although *d*-thyroxin has considerable activity. Later, C. R. Harington and W. T. Salter, of London (*Biochem. Jour.*, March-April, 1930, xxiv, p. 456), isolated *l*-thyroxin from the thyroid by digestion with trypsin and pepsin, and they conclude that there is no doubt that thyroxin exists in the gland "in peptide combination—as a constituent amino-acid, in fact, of the characteristic thyroid protein, iodothyroglobulin." When given to rats by the oral route, the digest that contained no iodine compound besides thyroxin caused a great increase in oxygen consumption, while equivalent amounts of *l*-thy-

roxin were without effect. Subcutaneous use of *l*-thyroxin was nearly as effective as the digest. Harington also holds the view "that there are only two iodine-containing compounds in the thyroid gland, namely, thyroxin and 3:5 diiodotyrosine"; and there are about equal amounts of iodine in each. However, it happens that only the thyroxin iodine is physiologically active.

CLINICAL COMPARISONS—The comparative therapeutic merits of thyroid extract and thyroxin have been the subject of much discussion. The technical perfection of the latter and the relative crudity of the "pharmacopœial extracts" have led Kendall and others to conclude that thyroxin is superior. However, despite the known potency of the Kendall principle, and also the fact that Harington's successes have opened the way to prepare a much less expensive but effective synthetic product, thyroid extract is still far more widely used as a remedy, for it is clear that thyroxin does not represent the entire thyroid gland.

In fact, A. T. Cameron, of the University of Winnipeg, insists that thyroxin shows from 25 to 50 per cent. of the activity of desiccated thyroid of similar iodine content when tested by its effect upon the growth of young rats. Also, this same writer, with J. Carmichael (*Jour. Biol. Chem.*, March, 1921, xlvi, p. 35), makes the remark: "Compared on the basis of iodine content, thyroxin is not nearly so effective as thyroid." And in the *Canadian Medical Association Journal* (May, 1924, xiv, p. 407) Cameron expresses this opinion:

"Since, according to Kendall, thyroxin only represents about one-quarter of the thyroid iodine, this reduces its relative effectiveness to probably not more than one-eighth of that of a corresponding amount of thyroid, even when the thyroxin is injected."

Again, Reid Hunt, now of Harvard University ("Glandular Therapy," Chicago, American Medical Association, 1925, p. 24), after admitting that thyroxin has an advantage in that it can be given intravenously and is, of course, of undoubted potency, adds:

"Animal experiments show that thyroxin is in some of its effects less active, even by intravenous injection, than thyroid administered by mouth, the drugs being given in doses containing equal amounts of iodine. . . .

"A total dose of 10 mg. of thyroxin, given intravenously, is said to bring the basal metabolism in myxedema from about −30 to normal; Sturgis found that 2.34 Gm. of the U.S.P. thyroid, given in divided doses to a patient with myxedema, raised the metabolism in six days from −32 to +4. Ten milligrams of thyroxin contains 6.5 mg. of iodine, and 2.34 Gm. of U.S.P. thyroid, 4.67 mg. of iodine."

Therefore, the pharmacopœial thyroid is more efficacious on a basis of iodine content, and in the same book Kendall's associates at the Mayo Clinic, H. S. Plummer and W. N. Boothby (page 32), state that they "prefer for oral administration desiccated thyroid standardized on its iodine content."

It is very evident that the thyroid gland contains a number of active substances with differing physiologic effects. Some of the recent work of Kendall emphasizes this (*Jour. Biol. Chem.*, Dec., 1928, lxxx, p. 357). He reports having studied six samples of desiccated thyroid, all of known physiological activity (determined by feeding experiments on thyroidectomized swine), and thyroxin could be isolated from but one of them. When it is recalled that only a very small amount of crystalline thyroxin can be isolated from such an amount of desiccated thyroid, it is clear that we must agree with Kendall that "it becomes evident that the thyroxin accounts for only a part of the increase in the basal metabolism."

Later in this same communication (*ibid.*, p. 373), Kendall postulates the existence in the gland of a form of thyroxin that he calls "active thyroxin." He does this to explain the discrepancy between the therapeutic activity of various extracts of the gland and the amounts of thyroxin that it is possible to isolate from corresponding quantities of it.

Studies have been made by K. Schulhof and collaborators in Chicago for the purpose of determining the nature of the substance or substances actually secreted by the thyroid. They utilized the precipitin reaction in testing for active principles in the blood and lymph. By this means they have demonstrated the presence of thyroglobulin, but not of thyroxin, in the thyroid blood and lymph. Concerning this, Schulhof (*Am. Jour. Physiol.*, May, 1930, xciii, p. 170) says:

"The presence of thyroglobulin in the lymph and blood from the thyroid gland has been established, while there is no evidence for the actual secretion of free thyroxin. It is possible that the latter is split off from the thyroglobulin in the blood or organs, but thyroglobulin may have other active groups than thyroxin."

Schulhof considers it suggestive that thyroglobulin has a high sulphur content, perhaps carrying physiological activity with it. And yet, all the activity of the dried thyroid can hardly be accounted for by its thyroglobulin content.

There are many "thyroid extracts" on the market, some of them plain desiccations of thyroid tissue; others processed by certain fractional solvent methods. Two thyroid concentrates are in use in America which represent the whole thyroid gland from which an additional quantity of inert material has been removed. Thyroprotein contains 0.33 per cent. of titratable iodine,

and Endothyrin* represents 0.4 per cent. In the case of the latter, feeding experiments demonstrate that the débris discarded during the concentration is indeed inert and also virtually free from iodine. Both of these preparations are available in solution for intramuscular injection, and, for some unaccountable reason, there is 125 times more titratable iodine in Endothyrin, the figures being: thyroprotein 0.0004 per cent. and Endothyrin 0.05 per cent. of organically combined iodine.

H. L. Baker and his associates, of Chicago (*Am. Jour. Physiol.*, June, 1930, xciii, p. 630), report having separated from normal thyroid glands a potent product with an unusually low iodine content, which has the following properties: (a) increases the blood-pressure; (b) slows heart rate; (c) increases blood sugar; (d) lowers the CO_2 capacity of the blood; (e) has no effect on the blood calcium. These properties are not due to either thyroxin or diiodotyrosine.

Quite recently in Germany there has been published a series of articles referring to a new and allegedly different thyroid product known as "Elityran." This preparation has been perfected in order to influence the thyroid features of obesity without bringing about such marked thyroidism as is commonly the case (79). It is said that this remedy contains from seven to ten parts of iodine per thousand, or 1/80 of the iodine content of thyroxin. Nevertheless, according to Carl Noorden, of Vienna, Elityran is clinically much more effective than thyroxin.

STANDARDIZATION—Since there is no single chemical test available for thyroxin, methods of assay have presented some difficulties. Inasmuch as the activity of the gland seems dependent upon the iodine content, quantitative determination of the iodine content of samples has been depended upon to a large extent in determining the therapeutic value of thyroid substance. Kendall and his associates have developed a very satisfactory method for iodine determination in animal tissues (*Jour. Biol. Chem.*, Aug., 1920, xliii, p. 149). This method of standardization, however, does not permit the detection of adulteration with iodine of non-thyroid origin, and proof that the pharmacological action of thyroid substance parallels the iodine content is not conclusive.

Fresh thyroid glands show a seasonal variation. The U.S.P. and B.P. desiccated thyroid substances are standardized to contain from 0.17 to 0.23 per cent. iodine. Harington has suggested that the thyroxin iodine should be 0.09 plus or minus 0.01 per cent. and that the inorganic iodine extractable with water should be not more than 10 per cent. of the total iodine (*Quart. Jour. Pharm. and Pharmacol.*, Oct.-Dec., 1929, ii, p. 501).

Comparative values of the different biological methods of standardization have been studied by many. Among the earliest methods suggested are those of J. M. Rogoff, of Cleveland (*Jour. Pharmacol. and Exper. Therap.*, Sept., 1917, x, p. 199) and J. F. Gudernatsch, of New York (*Anat. Rec.*, 1917, xi, p. 357), both based on the discovery by the latter that thyroid hastens amphibian metamorphosis. Rogoff used tadpoles and others have suggested axolotls. Swingle, among others, has shown that the test is not sufficiently specific since many organic iodine compounds, including acetyl-thyroxin, diiodotyrosine, and iodized proteins, such as iodoserumglobulin, cause metamorphosis but no physiological effect in mammals. Apparently they respond to the administration of certain types of organic iodine which are not of thyroid origin.

A generally accepted test is the acetonitril test of Reid Hunt (*U. S. Public Health Rep.*, July 10, 1925, Reprint No. 1026). It happens that the feeding of thyroid extract to mice influences markedly their resistance to the poison, acetonitril. The lethal dose and the quantity of thyroid necessary to double this dose are determined. This is usually about 10 mg. of a desiccation containing 0.2 per cent. iodine, and is administered by stomach-tube twenty-four hours previous to the intravenous administration of the acetonitril. Some other substances in doses hundreds of times as large as the thyroid dosage give a moderate degree of protection, but nothing apparently causes a response resembling that which follows the administration of thyroid sufficiently to interfere seriously with Reid Hunt's test.

An inhibitory effect of thyroid on the growth of young animals has been investigated by several. A. T. Cameron, of Winnipeg (*Proc. XIth Internat. Physiol. Cong.*, July 23-27, 1923), showed that thyroid feeding to young rats causes diminished growth rate, hypertrophy of the principal organs, and a resting state in the thyroid. H. Kreitmair, of Darmstadt (*Ztschr. f. d. ges. exp. Med.*, Jan. 19, 1928, lxi, p. 202), used young guinea-pigs and defined a "guinea-pig unit" as the smallest amount of material fed daily for six days to pigs of from 250 to 300 Gm. weight, which in three out of four pigs would cause a weight reduction of at least 10 per cent. This quantity divided into 1 Gm. equals the number of units in the preparation.

The possibility of developing a method of standardization based on the capacity of thyroid to relieve the symptoms of cretinism has been suggested. H. D. Caylor and C. F. Schlotthauer, of the Mayo Foundation (*Am. Jour. Physiol.*, Dec., 1926, lxxix, p. 141), found pigs very good subjects since they show quick response to thyroidectomy without troublesome parathyroid tetany. The increase in basal metabolism due to thyroid administration could be adapted to quantitative procedure.

ADMINISTRATION—Early experience with thyroid therapy (1891) involved its administration as an accessory food—by mouth. Later, the first pharmaceutical product was a glycerin extract, and soon after (1892-1893) desiccations were available in powder and tablets. Of course, the majority of these were given by mouth, though some of the early glycerin extracts were injected.

The dosage of thyroid preparations does not depend so much upon the amount given or even its potency, as upon factors present in the patient—the facility with which it is assimilated, the physiologic responsiveness (chiefly of the thyroid gland itself), and the physiologic need or "hunger" for this missing principle (see page 66).

Thyroid extract is given for two reasons: (1) to replace a lack (substitution), and (2) to encourage the thyroid itself (homostimulation). There is no question in any quarter about the former, but not all agree on the latter. In fact, quite recently C. R. Moore, of the University of Chicago (*Jour. Am. Med. Assn.,* Aug. 22, 1931, xcvii, p. 521), expresses frank doubt that such is possible. To me, the essence of every-day organotherapy chiefly concerns the rehabilitation of lazy or defective endocrines. Replacement therapy may be wonderful enough, but it has no end, as the myxedematous or diabetic patient knows full well.

Any clinician who has had any extended experience with organotherapy, and especially thyroid therapy, knows that the hormones act as catalysts and that sometimes the larger part of the response to therapy in a given case *clearly comes from the patient's own gland.* Obviously, the response of the gland itself will depend upon its physiological status—some thyroids are decidedly sensitive while others are as decidedly apathetic. This, indeed, is the basis for my own Thyroid Function Test (31).

Consequently, there can be no hard and fast rules for the administration of thyroid. The proper dosage is "enough," and this figure may actually vary at different times in the same patient. Variations of the response in the same patient are logically explained by assuming that the patient's own thyroid is functioning better—under the homostimulative action of the administered thyroid substance. (See the consideration of "Thyroid Instability" in Chapter 63.)

Further than this, digestion and assimilation differ in different persons and in the same person at different times. This can and does make a difference in the effectiveness of oral organotherapy (see page 64) and is one of the talking points in favor of thyroxin, which can be given "in exact dosage intravenously." But unfortunately, as we have seen, thyroxin represents only a share of the thyroid activity.

The way to overcome these difficulties is "to carry empiricism to the limit"—treat every case as a new one. Start with the Thyroid Function Test itself; feel your way; use the step-ladder method of dosage; and keep the patient under close observation. Do not give thyroid without pauses. Léopold-Lévi routinely omits it every seventh day. Carl von Noorden advises even longer rests. Finally, if the thyroid therapy must be continued over a long period, explain to the patient sufficiently so that he will be able to protect himself from the serious evils of thyroidism, which, far too often, are caused by medical thoughtlessness or carelessness.

THYROID PRODUCTS

ELITYRAN (1A)—A thyroglobulin prepared without heat, containing from 0.7 to 1 per cent. iodine, or about one-eightieth the amount found in thyroxin. Claimed to be ten times as active as thyroxin, compared on a basis of the iodine content. Used chiefly in obesity in doses of 150 mg. daily. *(I. G. Farbenindustrie A.-G., Berlin.)*

ELIXIR THYROIDEI—An aromatic elixir containing the active principles (iodothyrin and iodoglobulin) of fresh sheep thyroid. Each fluid dram contains 1½ gr. of dried thyroid. Dose: From 1 to 2 fluid drams. *(Squire & Sons, Ltd., London.)*

ENDOTHYRIN* (1A)—A concentrate of total thyroid gland from which sufficient additional cellular débris (inert by feeding experiments and containing virtually no iodine) has been removed so that the iodine content is not less than 0.4 per cent.—no iodine is added. In tablets of 0.03 Gm. (½ gr.). Dose: From 1 to 3 a day. Obtainable also in solution for intramuscular injection. Each cubic centimeter contains 0.05 per cent. titratable organic iodine and represents the active soluble constituents of 53 gr. of fresh thyroid tissue, with chlorbutanol 0.5 per cent.

IODOTHYRIN (1A) (Thyroiodine)—Dry milk-sugar trituration of the active constituent of thyroid gland. One Gm. iodothyrin contains 0.3 mg. (1/200 gr.) iodine, which equals 1 Gm. of the fresh gland. White or yellowish powder. Dose: Adults, from 1 to 2.5 Gm.; children, from 0.3 to 1 Gm. Maximum dose: From 2 to 4 Gm. *(E. Merck, Darmstadt.)*

THYRACOIDS—A preparation of iodothyroglobulin biologically standardized by the acetonitril test. In tablets of various doses. *(Reed & Carnrick.)*

THYRADEN (1A)—Standardized dried extract thyroid gland. Lactose trituration of the dried extract of thyroid gland; one part is equivalent to two parts of fresh gland; 1 Gm. contains 0.0007 Gm. (1/85 gr.) iodine. *(Knoll, Ludwigshafen.)*

THYREOIDIN (1A)—Dried and powdered thyroid glands of sheep; 0.4 Gm. (7 gr.) of the powder represents the active constituents of one fresh thyroid gland of medium size, *i.e.*, one part equals six parts of the fresh gland. Whitish powder, containing at least 0.18 per cent. organically combined iodine. In powder or tablets. Dose: From ½ to 1 gr. gradually increased (in rare cases) to 8 gr. two or three times a day. *(E. Merck, Darmstadt.)*

THYROID EXTRACT (1A)—*Thyroideum Siccum*, U.S.P. X—Dried thyroid glands of domesticated animals used as food by man, freed from connective tissue and fat, dried and powdered, and containing not less than 0.17 per cent. nor more than 0.23 per cent. iodine. Yellowish powder, one part of which is equivalent to five parts of fresh gland. Average dose: 1 gr.

THYROPROTEIN (1A)—A concentrated extract of thyroid gland adjusted to a definite organic iodine standard—0.33 per cent. In tablets of 1 per cent., 2 per cent., and 5 per cent. containing 1/50 gr., 1/25 gr., and 1/10 gr. of Thyroprotein, respectively. Dose: From 1/50 to 1/10 gr. Also in ampules containing 0.00125 Gm. (1/50 gr.) per cubic centimeter of Thyroprotein in physiologic salt solution with chloretone 0.5 per cent. *(Parke, Davis & Co.)*

THYROXIN (1A)—Tetra-iodo-oxyphenyl tyrosine. Active principle of thyroid gland. White or slightly yellow, needle-like, odorless crystals or powder; contains not less than 63 per cent. iodine. Has the same uses as dried thyroid. Dose: From 0.0002 to 0.002 Gm. (from 1/300 to 1/30 gr.). Average dose: 0.0005 Gm. (1/120 gr.). The smallest dose is always to be given, and increased by larger trial doses.

THYROXIN (ROCHE) (1A)—A synthetic product with an experimental action on metabolism stated to be exactly the same as that of the natural thyroxin. *(F. Hoffmann-LaRoche & Co.)*

Antithyroid Preparations

ANTITHYREOIDIN—A "thyroid serum" obtained from blood of thyroidectomized sheep, and preserved with 0.5 per cent. phenol. Amber-colored liquid. Uses: Exophthalmic goitre and dysthyroidism. Dose: In Basedow's disease, 0.5 cc. ***by mouth*** t.i.d. to begin with, increasing the dose by 0.5 cc. each day until it reaches 4 cc. single, and 12 cc., then reduce the dose in similar fashion. After a week or so, the treatment is repeated as before. From 60 to 100 cc. is ordinarily required for the average case. *(E. Merck, Darmstadt.)*

DIIODOTYROSIN (ROCHE)—A form of organic iodine obtained from the thyroid itself used instead of Lugol's solution in thyrotoxic conditions. Available in tablets of 0.1 Gm. Dose: From 1 to 3 a day. *(F. Hoffmann-LaRoche & Co.)*

THYROIDECTIN—A powder derived from the blood of thyroidectomized animals. Believed to supply to patients whose thyroids are abnormally active a substance that combines with the excess of thyroid secretion. Capsules of 0.3 Gm. (5 gr.). Dose: 1 or 2, t.i.d. *(Parke, Davis & Co.)*

III

ENDOCRINE DIAGNOSTICS

25. INTRODUCTION

In 1929 a book was published entitled "Endocrine Diagnostic Charts," in which the writer attempted to collate, in tabular form, data from various sources intended to facilitate endocrine diagnosis. As a colleague once said: "The difficulties of accurate endocrine diagnosis are the prime obstacles to the efficient application of organotherapy."

The complexity of many endocrine problems is due to the intricacies of the interrelation of the glands of internal secretion. Compensatory hyperfunction and even hypertrophy automatically follows dysfunction of one of these glands. The facility with which one endocrine organ assumes burdens that properly should be carried by another is at once the marvel of the research worker and the perturbation of the diagnostician.

Uniglandular manifestations are, of course, determinable, such as the muscular tire of hypoadrenia, the reduced metabolism of hypothyroidism, and the carbohydrate intolerance of hypopancreatism (diabetes). But it is rare to find any of these typical evidences of endocrine dysfunction alone. In fact, single-gland manifestations are so uncommon as to be almost rarities. The reason for this is that, before any functional difficulty localized in a given endocrine gland can exert any influence upon the rest of the body, it must also exert an influence upon the other endocrine glands; for the physiological contacts between the endocrines themselves are almost more numerous than the contacts between the endocrines and the rest of the body. Suffice it to say that endocrine diagnosis is neither simple nor easy, and that the majority of physicians concede that most of their failures in the treatment of endocrine problems are due to inadequate diagnoses.

With the wealth of books, reprints, and abstracts on the endocrines that are available in the Harrower Endocrine Library (see Chapter 110), one would suppose that it should be easy to find concise information regarding anything in endocrinology, but when it was suggested some years ago that we condense our present knowledge of endocrine diagnosis into a half dozen tables, it did not prove to be so easy.

As the task was begun, a number of tables already published in various places and languages were discovered, and it seemed that the most satisfactory plan was to use them. This is the reason why some of the following pages are devoted to Hutton's splendid tabular résumé, while others contain translations of publications by famous endocrinologists in Europe, and also why the excellent tabular arrangement of information about the pituitary disorders by Engelbach is used as a basis for the one found here.

It seemed advisable to give these much the same as they were originally published, with the exception of such changes as our newer knowledge has made necessary because, as the reader will see, each of these writers has considered the subject from his own special point of view and has gathered together the data in a very effective manner.

It should be stated here that quite the most effective means of establishing an endocrine diagnosis is *by successful treatment,* for nothing is more convincing than the change that follows the use of indicated organotherapy. It is self-evident, however, that the recognition of all existing endocrine faults and their correction by suitable endocrine therapy do not necessarily suffice to restore the health of a given patient. Many more things than glandular functions may be wrong, and therefore a careful and complete endocrine diagnosis does not lessen the necessity for obtaining a maximum of general diagnostic information. Indeed, it may be said without hesitation that the most successful organotherapeutists are those who get the most intimate and the broadest conception of what ails the patient, and who, in addition to removing the fundamental factors that cause these difficulties, can not only build or reestablish the deranged endocrine functions by suitable endocrine encouragement, but also correct the other ailments that are associated with the dyscrinic manifestations. And here the diagnostic acumen of the organotherapeutist is subjected to another test, for the relation between general systemic disease and endocrine dysfunction, or between involvement of any special organ and endocrine dysfunction, is not always the same. That is, the endocrine dysfunction may be either the primary or the secondary factor. Naturally, it makes a difference in the therapy of endocrine disturbances, and also in that of troubles in other organs, whether the endocrine dysfunction has been induced by trouble in a certain other organ or whether it has been instrumental in causing it. Especially necessary for diagnosis, therefore, is a complete history of the patient, and it is surprising how frequently an acute infection will be found to precede the manifestations of certain endocrine disabilities.

26. ETIOLOGICAL FACTORS

Heredity—Environment—Emotional Stress—Toxemia—Allergy, etc.—Drugs and Drug Addiction—Other Dyscrinisms—Cancer, etc.—Senility.

IN THE practice of medicine, success comes largely from the appreciation of causes rather than effects, and from the broader treatment that such added knowledge makes possible. It is just as wrong to treat endocrine symptoms and ignore their origin as it is to treat any disease only symptomatically. Unfortunately many of the fundamental factors underlying the true endocrine diseases are of such a nature that, while we may be convinced of their rôle, there is little we can do to change them. As Theodore Roosevelt once aptly said, "You can't unscramble eggs!"

However, the successful endocrinologist is the one who can uncover the reasons for the difficulties submitted to him, and who, while he is attempting to modify the dyscrinism and its immediate effects, naturally is making every effort to control the causes. Organotherapy very often fails in proportion to the extent of our view-point!

HEREDITY—Some endocrinopathic individuals are born that way; others become so. It may safely be said that the majority of the latter have a constitutional vulnerability in that direction so that there is at least a potential hereditary feature. The constitution with which we are born is really inherited, since it is transmitted to us by our progenitors. Congenital endocrinopathies, however, are those troubles that are acquired by the fetus in utero because of circumstances that have influenced the parents.

Among hereditary endocrinopathies, may be mentioned extreme hypothyroid conditions, such as myxedema and cretinism, which are notoriously familial afflictions. Cretinism tends to recur in a family, even in a locality where only a fraction of the community is affected. This leads to the conclusion that the constitutional hereditary factors play a part in determining the insufficiency of the thyroid gland in the presence of unfortunate environmental conditions. The cretin is such not merely because of an abnormal thyroid but also because of abnormal chromosomes that determine such an abnormal or peculiar thyroid—a thyroid that functions inadequately only when the environmental conditions are not at their best; in other words, a thyroid that is constitutionally sensitive to variations in the environment.

It is generally conceded that endocrine dissimilarities account quite largely for racial differences in both traits and appearance—a factor that is instanced by the subthyroid facies of the Mongolian and the hyperadrenal activity of the Caucasian. In diabetes mellitus, which is among the endocrine

diseases that are considered to be hereditary, there is not only a likelihood of a familial predisposition but even a racial predilection; *e.g.*, Jews are peculiarly prone to develop it. This, however, probably depends as much on their worrying, nervous disposition and their liking for rich and sweet foods, as on a diabetic diathesis proper.

Any anomaly that the growing fetus acquires because of unfavorable conditions (for instance, disease of the pregnant woman) is congenital, though not necessarily transmitted by heredity. These particular conditions, therefore, stand between the congenital (in the strict sense of the word) and the acquired endocrine disorders. They may be induced by severe infectious diseases suffered by the mother, such as smallpox, diphtheria, scarlet fever, etc., or they may be due especially to syphilis and other serious diseases. Goitre, or the tendency to it, undoubtedly is transmissible through the mother. Hypothyroidism in the pregnant woman should be treated and forestalled where possible, if only for the good such treatment will do to the unborn child.

Then there are certain toxic conditions—such as those that may induce pernicious vomiting and other forms of toxemia—which are prone to leave an impress upon the growing fetus. Undoubtedly, factors that cause dyscrinism in the mother are influencing the endocrines of the child in identically the same way. Diabetes mellitus in pregnant women must affect the offspring, though fortunately it is rare, because well-developed diabetes in women is prone to cause sterility. Whether diabetes as such is transmitted by heredity or not, it may be assumed that the functional ability of the infant's pancreas is at least impaired.

Deprivation such as was suffered during the Great War, especially in the central European countries, affected the children, who were born constitutionally deficient and relatively non-resistant to pathogenic factors. Many had an endocrinopathic inheritance thrust upon them which is only beginning to show itself now. It is a fortunate compensation that extreme deprivation and want often induce sterility by suppressing ovulation, otherwise even more war babies would have been born to increase the host of misfits. During famines and pandemics, the infants that manage to be born at term (there are many abortions and miscarriages) are defective in many ways.

ENVIRONMENT—During infancy and childhood, as well as during adolescence and adult life, environment is an important etiologic element.

Unsatisfactory housing (basements, tenements, crowded conditions, dampness, absence of light, etc.) tends to cause a stunted, incomplete development of the small child. Such factors cannot fail to influence the endocrines also, and the resultant dyscrinism makes bad worse.

The matter of diet is important too; and deprivation of food, or food deficient not only in its caloric content but in the essential food factors, will injure the endocrine system. This is particularly true of the vitamins, which many now believe are active largely through the endocrine glands (101).

Geographic and climatic conditions undoubtedly are factors. The effect of altitude upon asthma is well known. There are those who claim that similar conditions influence hyperthyroidism. It is an interesting observation that young and middle-aged women who move to Southern California become stout more readily than they do in their former homes. Perhaps it is California's wonderful climate! I know of one case that is virtually an experiment: A young woman nurse, who in her home in Oregon is moderately plump, is in good health, and menstruates regularly. As soon as she comes down here, amenorrhea develops, she becomes heavier, her mentality is dulled, and she seems to be not only markedly hypovarian but also hypothyroid and hypopituitary. She has gone back and forth repeatedly—always with the same result. However, there is another phase of climatology that is far more important: Caucasians who live in tropical countries often suffer with regard to their adrenals, which are apparently overstrained—for example, the syndrome of hypoadrenia is unusually frequent among Europeans in India. It is not known whether cases of thyroid upset and diabetes mellitus are more numerous in tropical countries, but some day more data will be available. It seems that diseases associated with insufficient hepatic functioning—of both the external and the internal hepatic secretions—are accentuated in hot climates.

Undoubtedly a different influence is exerted upon the endocrines by a strict vegetarian diet on the one hand, and a mixed or largely meat diet on the other. A very important factor is the completeness of the supply of the accessory food substances—the vitamins and the mineral salts—as may be seen in patients afflicted with deficiency diseases and in whom some of the endocrines are gravely depleted. The effectiveness of the digestive and assimilative apparatus enters here, but this point will be considered under the heading of toxemia of endogenous origin.

EMOTIONAL STRESS—Mental or emotional stress is a potent cause of endocrine troubles. The classical investigations of Walter B. Cannon, of Harvard, have shown the effects of emotional upset on the endocrine functions, and with the passing years these findings are becoming more and more accepted. ("Bodily Changes in Pain, Hunger, Fear, and Rage," New York, D. Appleton & Co., 1915.) Then there is the sinister influence of worry, shock, and apprehension, all of which are endocrine depletants, especially if

continued for a long time. The fatigue syndrome, which Edward Ochsner, of Chicago, described vividly some years ago ("Chronic Fatigue Intoxication," New York, G. E. Stechert & Co., 1923) and which is one phase of what has been called "shell-shock," is a condition of depleted emotional equilibrium in which the endocrines are decidedly concerned. Incidentally the writer was among the first to emphasize the essentially adrenal character of shell-shock and war neuroses. ("Shell-Shock and the Internal Secretions with Suggestions as to Treatment," *Prescriber,* Oct., 1916, x, p. 203.)

We are familiar with the nervous breakdown suffered by persons exposed to sudden fright, apprehension, and stress in general, for instance, the Iroquois fire in Chicago, or the San Francisco earthquake, many of the survivors of which have been neurasthenics ever since. Many who have passed through calamities like destructive fires, earthquakes, floods, and shipwrecks, always will show the results of fear, shock, and mental and emotional stress. The impress is upon the thyro-adrenal mechanism and, through it, on various other functions and organs. Exophthalmic goitre has been caused many times by fright alone.

TOXEMIA—Toxic conditions of all sorts exert a strain on the endocrines, more especially on the detoxicating glands: the liver, thyroid, parathyroids, and adrenals. *They are the outstanding causes of dyscrinism.* Toxemia may be of either endogenous or exogenous origin. The endogenous toxins originate in defective cell chemistry or in alimentary poisons, or they may be due to the gradual absorption of the bacterial protein products from foci of infection anywhere in the body. The consideration of such foci forms a connecting link with that of the exogenous toxins, because infectious foci may be produced by bacteria coming from without as well as by those bacteria that commonly exist within the body. One cannot say that they exist there normally, but they always exist there naturally; for instance, the bacteria present in the colon are facultatively pathogenic.

Very potent sources of toxic strain on the endocrine glands are presented by infectious foci in the tonsils and lymph nodes, in the appendix, in the ovaries and tubes in women, in the urethra and prostate in men, and elsewhere. The constant absorption of toxin from these foci entails a continued demand on the resources of the detoxicating endocrine glands, which in course of time may lead to exhaustion and then to a great many symptoms that may express themselves generally or locally.

Toxic material having its origin in an incomplete disintegration of food substances, especially proteins, is a frequent source of strain on those endocrine glands that have to do with detoxication.

There are two dissimilar aspects to this subject: (1) constitutional shortcomings in the nature of allergy, with the strange hypersensitiveness and idiosyncrasy to certain foods and proteins, and (2) defective detoxication by the mechanisms responsible for the purification of the blood stream.

The subject of allergy is considered separately (36) as is also hypohepatism (66). From an etiological view-point, however, defective hepatic detoxication is a very important cause of endocrine stress.

It is well known that detoxication by the liver is concerned particularly with the toxic products brought from the intestine through the portal vein. The detoxicating influence of the thyroid is directed more particularly against the poisons produced by bacteria that have invaded the body and against those substances that may have passed the liver barrier. The detoxicating action of the parathyroids is directed chiefly against the wastes, acid and amino-acid in nature, which these little glands are capable of modifying apparently through their spectacular regulation of the body's store of calcium.

The demands on these detoxicating organs commonly become so excessive as to break down their functioning ability. For instance, when excessive demands have been made on the liver for the production of the detoxicative hormone, which normally causes the disintegration of toxic products of incomplete protein cleavage, functional hypertension may result and, under certain conditions, hypotension may develop, either because of exhaustion of the pressor organs or because of initial constitutional peculiarities. This functional hypertension is thus closely associated with a depletion of one of the hepatic endocrine functions, which explains the efficacy of Anabolin* in such cases. (See page 330.) Similarly, extreme or unduly continued demands on the detoxicating resources of the thyroid or parathyroids, may cause these organs to become exhausted, with the development of certain typical clinical pictures, which are discussed elsewhere.

Exogenous toxins are produced in the course of infectious diseases and exert a most severe strain on the endocrine glands. The most spectacular instance is the depletion of the adrenal glands produced by the bacteria of influenza. This is responsible for the prostration characteristic of the disease; it also explains the protracted and slow convalescence, the tendency to relapse, and other peculiarities, especially the circulatory picture. The clinical results that follow the application of adrenal support confirm these conclusions (69).

It is known also that changes arise in the pituitary body during acute infections, and hypercolloidism has been found in this gland following experiences of this nature. Pituitary obesity has commenced after an attack of scarlet fever in early childhood, and frequently one can trace major signs of hypopituitarism to acute infections, infectious diseases, or poisoning.

DRUGS AND DRUG ADDICTION—It is a natural assumption that the endocrine glands are influenced by drugs, the effect of which may be either beneficial or detrimental. Early studies on this subject will be found in Sajous' book ("The Internal Secretions and the Principles of Medicine," 1908, Volume II, Chapters 18 to 22), where he enumerates and describes drugs that stimulate the endocrine glands, that enhance the defensive properties of the blood, and that depress the functions of the adrenal, vasomotor, and sympathetic centers. Many drugs, in suitable doses, will promote and encourage the endocrine functions. Any harmful effect necessarily is dependent on doses larger than required and sufficient to overtax the ability of the glands to respond. Some of these drugs undoubtedly can act as do the intestinal poisons, by causing overexertion of the endocrine functions, which at first induce excessive functioning and then a corresponding functional depletion.

I am convinced that the use of strychnine, coffee, and tonic alkaloids add to the stress on the endocrines as a whole. Walter C. Alvarez, of the Mayo Foundation, in his recent book, "Nervous Indigestion" (New York, Paul Hoeber, Inc., 1930), makes the following remark about the use of strychnine, which has a bearing on this:

"Many physicians give strychnine to nervous patients but from what I can learn of its pharmacologic action it seems to me that it should be the last drug on earth to give to these persons. They are already on edge, with reflexes exaggerated, senses overly acute, and the doorways to brain and cord open to every incoming stimulus. What is wanted is some derivative of bromine or barbituric acid that will somewhat close the doors, raise the threshold, and quiet the reflexes, and not a drug like strychnine, which is preeminently a connector of nervous pathways. The dog that has been poisoned with strychnine has his nervous system so sensitized that even a sudden sound or a breath of cool air on his ear will suffice to throw him into a convulsion."

There are certain drugs, however, that almost invariably exert pernicious effects, at least when taken habitually and in large doses. It has been observed clinically that the immoderate use of alcohol, coffee, and tobacco, prevents the beneficial action of adrenal therapy. The conclusion is justified that, if taken in excess, they will depress adrenal functioning; and this is borne out by Sajous and many others. The same result follows the habitual use of narcotics and even of the non-narcotic sedatives. This is the reason why drug addicts usually show such marked muscular atonia and such very low blood-pressure. As will be seen elsewhere (75), there are real possibilities for the support of the depleted adrenals during the stormy withdrawal period in the treatment of drug addicts.

OTHER DYSCRINISMS—It is a common observation, and an undoubted physiological fact, that any disturbance of the endocrine equilibrium will produce consequences. If, for instance, one endocrine organ is diseased and its activity impaired, or if it is removed, its synergistic endocrine glands will be induced to overact; and its antagonists, being no longer checked or restrained, will also tend to function to excess. As we have already seen, the best-known instance of this kind is the gradual or abrupt elimination of the ovarian internal secretions either during the change of life or by operation. It is a common observation that the two glands that are intimately associated with the ovaries, namely, the pituitary and the thyroid, are incited to unusual exertion which sometimes is so great as to bring about exhaustion. This may explain the symptoms of pluriglandular defect that so frequently develop in relation to the menopause, the best-known of which are climacteric obesity and myxedema. Again, it is frequently noted that removal of the ovaries in experiment animals as well as in women, may be followed by permanent hyperplasia of the pituitary.

Disease, especially a hyperplastic tumor of the adrenal cortex, may whip up the gonads to precocious development in children or it may change the feminine peculiarities in women to masculine traits (virilism, hirsutism). Pineal tumor has also been claimed by some writers to be responsible for precocious puberty in small children, especially boys.

Another instance of an influence on certain endocrine organs, through the elimination of others, is the fact that, physiologically, the thymus commences its involution in infancy and is supposed to complete it at the fifth or seventh year, thereby removing its check on the development of the genital organs. If the thymus persists instead of undergoing its physiological involution and if in consequence gonad development is delayed and impaired, abnormal development of the total organism results. The so-called "thymocentric" persons are never normal.

Processes that are of themselves physiological, also may become responsible for glandular changes. An interesting instance comes to mind: In pregnancy the anterior portion of the pituitary usually shows a multiplication of large neutrophilic elements, which apparently are derived from the normal cells. After delivery, the gland involutes but, it is claimed, never goes back to its previous size. This change, occurring in successive pregnancies, may bring about a physiologically inactive condition of the gland and may produce the adiposity, loss of hair, asthenia, and subnormal temperature often seen in women who have had many pregnancies. On the other hand, overactivity may persist, leading first to acromegalic changes with a final condition of pituitary insufficiency.

There are many other endocrine reactions to various circumstances encountered in health and disease—in fact, these glands are peculiarly responsive to practically all kinds of stimuli—but it must suffice here to say that *one glandular upset always causes another.*

CANCER, ETC.—The endocrine glands are subject to malignant disease, as are all other tissues of the body. Even when the glands themselves are not actually the subject of malignancy, their functioning necessarily is impaired by the devitalizing results of malignant disease elsewhere in the body, especially by the resulting cachexia. Addison's disease, a classic adrenal picture, is certainly a tumor whether it is due to tuberculosis, as most of us believe, or to cancer. The effects of tumor in the adrenal cortex and in the pineal have already been mentioned. Tumor formation in the hypophysis may be malignant or benign, but it causes many essentially pituitary symptoms as well as the so-called "neighborhood" pressure symptoms outlined fully in Chapter 30.

Unfortunately, such developments do not lend themselves to treatment even though, as the reader will see further on, it is possible to mitigate the results and to interfere with the reactions to such end-conditions by means of organotherapy.

SENILITY—Arnold Lorand, of Carlsbad, and several other writers call old age a disease. Serge Voronoff, of Paris, whose studies are epoch-making even though his methods may not be so well appreciated, describes aging as due to a gradual increase of the connective-tissue cells which replace the "noble" tissue cells, preventing their regeneration. This unphysiological increase of connective-tissue cells impairs the vitality and functioning ability of all endocrine glands as it does with relation to other organs. It lessens the production of internal secretions and is thereby responsible for the waning strength and energy, both physical and mental, and the increased fatigability of the organism so characteristic of old age. The metabolic processes are gradually slowed down; in short, the organism becomes old. As will be seen in Chapter 88, senility is characterized by increasing deficiency in all endocrine functions. Presenility, resembling senility in all respects save the age incidence, is essentially a manifestation of endocrine depletion—hypocrinism.

27. AN OUTLINE OF THE ENDOCRINE DISORDERS

(After that of Dr. James H. Hutton, of Chicago)

THE THYROID GLAND

Thyroid Hypofunction—Hypothyroidism

ENDOCRINE FINDINGS	Thyroid aplastic or atrophied, or colloid goitre. No increased sensitiveness to epinephrine. Thyroid extract well tolerated. Compensatory pituitary hypertrophy probable.
APPEARANCE	
Skin (Nails and Hair)	Skin yellow like parchment or pale like alabaster. Malar flush. Myxedema. Nails thick, rough, wrinkled, dry, brittle, with white spots and longitudinal ridges. Extremities cold. Dermatoses common. Hair dry, scanty, brittle, lusterless. Outer third of eyebrows missing. Scant hairiness of the arms and legs. Perspiration reduced. When condition occurs early, teeth are irregular and of poor quality.
Structure (Bones, Muscles)	Retarded bony growth. Defective development of ossification centers. Short, thick, or deformed bones (fingers with blunt ends). "Rheumatism." Stiff joints, cracking noises in joints. Flatfoot very common.
CLINICAL FINDINGS	
Circulatory	Bradycardia; hypotension or hypertension. Constant chilliness; "dead" fingers. Sensitiveness to cold. Enjoy heat. Circulation poor.
Alimentary	Appetite poor or variable. Thick, coated tongue; dry mouth; hypocholia; constipation, gas, ptosis. Teeth soft, carious; pyorrhea common.
Respiratory	Respiratory oppression, slow respiratory rate. Asthma-like attacks. Occasionally symptoms of pressure on the recurrent laryngeal nerve.
Nervous	Apathy; poverty of thought and initiative; drowsiness; psychomotor retardation; melancholia. Marked sensations of cold. Asthenia. Headache dull and of early-morning type. Reflexes reduced or absent.
Urogenital	Early puberty. Menses usually regular, profuse, painless. Amenorrhea occasionally; more often infiltration and menorrhagia. Diminished libido and potentia sexualis. Nocturnal enuresis and cystic irritability.

Special Sense	Deep-set eyes (enophthalmos); narrow lid slits; thickened lids. Tinnitus; otosclerosis. Giddiness. Nasal "catarrh." (Incipient cataract has improved under thyroid medication.)
LAB. FINDINGS	
Urine	Variable output; low in solids and urea; high acidity; indican + +; many squamous epithelia.
Blood	Anemia usual. Leukopenia; lymphocytosis. Eosinophilia common.
Metabolism	Basal metabolic rate below normal. Obesity with general distribution; padding on dorsum of hands and feet, also in supraclavicular and dorsal cervical regions. Increased carbohydrate tolerance. Hypothermia. Blood calcium usually below normal but has no diagnostic import.

Thyroid Hyperfunction—Hyperthyroidism

ENDOCRINE FINDINGS	Smooth, diffuse, symmetrical, vascular enlargement of the thyroid in Graves' disease. A nodular goitre in adenoma with hyperthyroidism. Hypersensitiveness to epinephrine and to thyroid extract. Persistent thymus or hypertrophy of lymphoid tissue generally.
APPEARANCE	
Skin	Thin, soft, moist skin. Circulation good; occasionally mottled erythema of neck and chest. Hair smooth, silky. Perspiration increased. Cutaneous excitability. Nails smooth and not brittle.
Structure	Delicate skeletal structure. Long, slender fingers. Increased mobility of joints. (Adenoma with hyperthyroidism occurs in persons of any skeletal build.)
CLINICAL FINDINGS	
Circulatory	Tachycardia; palpitation; vasomotor irregularities. Hypertension common in toxic adenoma; high pulse pressure in Graves' disease.
Alimentary	Tongue variable. Attacks of diarrhea and vomiting with no apparent cause. "Nervous indigestion." Occasional constipation (spastic). Good appetite with loss of weight.
Respiratory	Shallow breathing; tachypnea; feelings of dyspnea.
Nervous	Nervous irritability extreme. Restlessness; apprehension; anxiety (phobias, obsessions). Insomnia. Psychomotor activity; fine tremor of hands and tongue. Sensations of heat, flushings, and intolerance

to heat. Headache common ("pounding"). Reflexes increased.

Urogenital — Amenorrhea; occasionally diminished libido and potentia sexualis.

Special Sense — Exophthalmos; wide lid slits. Von Graefe's, Möbius', and Dalrymple's signs. (Swollen eyelids, pigmented lids.) Hearing sensitive.

LAB. FINDINGS

Urine — Polyuria; average solids and elimination.

Blood — Normal red count. Lymphocytosis, relative. (Said to occur in both hypo- and hyperthyroidism, but is more constant in hypothyroidism.) Eosinophilia occasional.

Metabolism — B.M.R. increased. Undernutrition. Diminished CH tolerance. Temperature may be increased. Pulse pressure increased by a lowering of the diastolic. This occurs most commonly in Graves' disease. The systolic pressure is frequently elevated in adenoma with hyperthyroidism, and is frequently mistaken for heart disease or hypertension.

THE PITUITARY GLAND—HYPOPHYSIS

Pituitary Hypofunction—Hypopituitarism

ENDOCRINE FINDINGS

(L†) Gland in the sella turcica small, stalk often not seen, and clinoid processes inverted. Gonad dysfunction and atrophy usual. Hypothyroidism common, in both early and late types.

(T†) With tumor, gland enlarged, clinoids eroded.

APPEARANCE

Skin — Skin delicate, thin, and pale. Hair thin and silky, reduced in axillæ, on mons, etc. Nails thin, lunulæ small. Teeth irregular, superimposed.

Structure

(E†) Stature short. Bones small and slight. Dwarfism. General adiposity. Skeletal form puerile.

(L) Growth changes negligible. Adiposity marked. Female form of pelvis in males. Muscles normal or small.

CLINICAL FINDINGS

Circulatory — Circulation poor, pulse slow. Blood-pressure low or normal.

†E, early or prepuberal; L, late or postpuberal; T, pituitary tumor.

Alimentary
Constipation, intestinal stasis and atony.
(T) Severe vomiting, irregular in onset, often of projectile type.

Nervous
(E) Mentality normal.
(L) Apathy, psychasthenia, somnolence, vagotonia. Lack of strength and endurance.
(T) Headaches, epileptoid attacks, "uncinate fits."
(E) Secondary sex manifestations absent in prepuberal cases; hypogenitalism.
(L) Gonad development not abnormal, but function depleted.

Urogenital
Loss of libido and potentia in male. In female, loss of libido, amenorrhea or menorrhagia.

Special Sense
Nasal outlets often unduly small. Sinuses small.
(T) Eyes affected by local tumor pressure—bitemporal hemianopsia. Later, choked disc and optic atrophy. Strabismus.
Hearing normal.

LAB. FINDINGS
Urine
Normal; polyuria with posterior insufficiency.

Blood
Lymphocytosis common.

Metabolism
B.M.R. and CH tolerance normal. Temperature subnormal.

Pituitary Hyperfunction—Hyperpituitarism

ENDOCRINE FINDINGS
(E) Large pituitary gland, thick stalk, flaring clinoid processes. Gonad hypertrophy.
(L) Secondary functional gonad inefficiency though usually not atrophy. Hyperthyroidism occasional.
(T) Gland very large, clinoids completely eroded. Head bones very thick.

APPEARANCE
Skin
Skin thick, dense, and hypertrophic. Hair thick and coarse. Hypertrichosis and, in female, of masculine distribution.

Structure
(E) Gigantism, excessive length of long bones.
(L) Acromegaly, osseous growth prominent in face (prognathism), hands, and feet. Bones heavy, with exostoses common. Pelvis in women often of masculine type. Musculature well developed.

CLINICAL FINDINGS
Circulatory
Blood-pressure frequently increased, (L) reduced afterwards. Pulse may be increased.

Alimentary	Digestive upsets common. Tendency to spasticity. (T) Vomiting, as above.
Nervous	(E) Apathy and somnolence. (L) Hyperactive mentality, temperamental irritability, mental instability. (T) As outlined above.
Urogenital	(E) Hypertrophy of genitalia, occasional sexual hyperexcitability, menses usually not much increased. (L) Hypogonadism, but sex development normal or plus.
Special Sense	Nose large, alæ flaring; sinuses large. Eye findings in tumor as outlined above. Hearing often very acute.
LAB. FINDINGS	
Urine	Glycosuria.
Blood	Lymphocytosis usual. Eosinophilia often found.
Metabolism	CH tolerance normal or somewhat decreased. Temperature normal.

THE PINEAL BODY—EPIPHYSIS

Hyperpinealism—Pineal Tumor

ENDOCRINE FINDINGS	Hypergenitalism; pressure effect upon pituitary causing pituitary symptoms (?)
APPEARANCE	
Skin	In children, precocious growth of hair.
Structure	Abnormal height and muscular development.
CLINICAL DIAGNOSIS	
Alimentary	Vomiting.
Nervous	*General* (brain). Increased intracranial pressure (internal hydrocephalus) with headache, vertigo, drowsiness, mental changes, choked disc. *Neighborhood* (tumor). Midbrain involvement causing various cranial nerve palsies, especially III, IV, VI, with diplopia. (Cerebral peduncle involvement with lesion in pyramidal tract.)
Urogenital	Premature puberty with hyperplasia of genitalia.
Special Sense	Secondarily affected by cranial nerve lesion.
LAB. FINDINGS	
Metabolism	Obesity. Less commonly cachexia and emaciation. Increased CH tolerance.

THE ADRENAL GLANDS

Addison's Disease—Hypoadrenia

ENDOCRINE FINDINGS	Various disturbances common to other glands. *Status thymicolymphaticus*. Hypogenitalism. Goitre. Dyspituitarism.
APPEARANCE	
Skin	Skin and mucosa pigmented (from dirty yellow to dark brown), usually diffuse but accentuated on face and neck, in axillæ, about nipples, genitals, extensor surfaces of joints, and parts exposed to pressure. Dermographia (Sergent's white adrenal line).
Structure	Muscular asthenia extreme. Myotonia. Lumbar pains, occasionally one-sided.
CLINICAL DIAGNOSIS	
Circulatory	Hyposphyxia (Martinet). Arterial hypotension; myocardial weakness. Syncope common. Vascular hypoplasia.
Alimentary	Meteorism; abdominal pain and tenderness; anorexia; nausea; vomiting; alternating constipation and diarrhea.
Respiratory	Subjective feelings of dyspnea. Shallow breathing. Acute tuberculous lesions often present or scars of old lesions usual.
Nervous	Asthenia; stupor; drowsiness; insomnia frequent. Memory defects (excitation; irritability). Fainting spells.
Urogenital	Hypogenitalism.
Special Sense	Asthenopia.
LAB. FINDINGS	
Urine	Defective output; reduced solids; high acidity; indican +++.
Blood	Moderate secondary anemia. Relatively high lymphocytosis.
Metabolism	Undernutrition. Hypoglycemia with increased CH tolerance (occasionally decreased). Reduced basal metabolic rate. The clinical syndrome of hypoadrenia presents symptoms similar to those of Addison's disease, but milder in form and degree. It is due to infection—general or focal, acute or chronic—prolonged mental or physical strain, or the overdosage of drugs such as arsenic or mercury as in the treatment of syphilis.

ADRENAL CORTEX—INTERRENALS

Hyperfunction—Hypernephroma

ENDOCRINE FINDINGS	Adrenal cortex hyperplasia, aberrant interrenal bodies, and interrenal tumors (not detectable early). More common in the female, in whom they tend to produce male characteristics.	
APPEARANCE		
Skin	*Prepuberal*	*Adult*
	Premature development of hair. Acne; skin rough and coarse.	Hirsutism. Women show mustaches and beards and triangular arrangement of pubic hair with marked general hypertrichosis. General or patchy pigmentation. Acne.
Structure	Unusually rapid growth. Abnormal strength (Herculean infants).	Increased physical strength. Virilism ("masculine women").
CLINICAL DIAGNOSIS		
Circulatory		Skin warm and well vascularized.
Alimentary	Vomiting and diarrhea in late stages.	Nausea and vomiting in late stages.
Respiratory		Voice heavy and masculine.
Nervous	Abnormal psychomotor activity.	Egotistic, overbearing, irritable.
Urogenital	Pubertas præcox, including premature enlargement of genitalia; in young girls, mammary gland development and menstruation; in small boys, erections, pollutions, and change of voice years before such changes are due.	Irregularity of menstruation; amenorrhea. Unusually strong excitability. Hypertrophy of clitoris. Frigidity in late stage.
LAB. FINDINGS		
Metabolism	Obesity, especially of hips and abdomen. Rapid growth (emaciation and cachexia later).	Obesity common.

THE SEX GLANDS

Hypergonadism

	Male	*Female*
ENDOCRINE FINDINGS	Tumors of testes; gonad hypertrophy. Pituitary disease.	Tumors of ovary; enlarged external genitalia.
APPEARANCE		
Skin	Early secondary sex characteristics (hair growth).	Similar.
Structure	Rapid growth, early epiphyseal closure, premature ossification.	Similar.
CLINICAL DIAGNOSIS		
Circulatory	Erethism; emissions.	Erethism; prolonged menses.
Alimentary	Hyperpepsia common; digestive instability.	Similar.
Respiratory	Early voice changes.	
Nervous	Mentality modified by premature sex development. Temperamental imbalance.	Similar.
Urogenital	Genitalia overdeveloped; premature puberty (pubertas præcox).	Early menses.
LAB. FINDINGS		
Blood		
Metabolism	Increased.	Increased.

—THE GONADS

Hypogonadism

Male— Eunuch	*Male*— Eunuchoid	*Female*
Agonadia (castration). Small thyroid. Pituitary often enlarged.	Gonads aplastic or hypoplastic. Other endocrines involved, especially pituitary.	Ovariectomy. Natural or premature menopause.
Skin pale, sallow, wrinkled. Hypotrichosis. Feminine hair distribution.	Pale, delicate, finely wrinkled. Hypotrichosis (feminine type).	Lack of secondary sex hair growth.
Tall, thin type; arms and legs longer. Broad pelvis. Delayed epiphyseal union.	Similar.	Increased height before puberty. Long arms and legs. Long, thin hands.
Vasomotor atonicity; cold, clammy extremities.	Similar.	Vasomotor disturbances (as in menopause).
Variable findings.	Similar.	Digestive imbalance. Nausea and vomiting as in early pregnancy.
Small larynx; child-like soprano voice.	Similar if originating early.	Colds common at periods.
Non-aggressive, neurasthenic state. Depression, fears, and phobias.	Lack of normal emotions and will-power. Dull, relaxed, clumsy.	Nervousness; anxiety states; psychoses. Depression at menses. Paresthesias, etc.
Castration early: other sex organs hypoplastic, no sex impulse. Castration late: prostatic atrophy; gradual loss of potentia and libido.	Hypoplastic gonads; cryptorchidism; sterility; libido and potentia diminished or absent.	Before puberty: infantile genitals and secondary sex characters. No mammary development. Amenorrhea and dysmenorrhea.
Anemia usual.		Secondary anemia.
B.M.R. low. Fat deposits on lower abdomen, buttocks, and breasts; trochanteric obesity.	Trochanteric obesity after 35. More often thinness. Low B.M.R.	Trochanteric obesity after 35.

THE PARATHYROID GLANDS

Parathyroid Hypofunction—Hypoparathyroidism

ENDOCRINE FINDINGS	Parathyroids removed with thyroid. Hypoparathyroidism following thyroidectomy.
APPEARANCE	
Skin	Pallor of skin; dermographia; erythema. Angioneurotic edema. Nails brittle, ridged. Hair thin.
Structure	Defective growth of bones. Cramps of muscles; carpopedal spasm. "Obstetric hand" with flexure of wrists.
CLINICAL DIAGNOSIS	
Circulatory	Vasomotor disorders. Subnormal temperature; chilly sensation. Palpitation and shortness of breath.
Alimentary	Functional digestive upsets, as hyperchlorhydria, pylorospasm, or diarrhea. Defective soft teeth, dental caries. Gastric tetany. Acute dilatation of stomach.
Respiratory	Tetany often induced by deep breathing. Laryngospasm.
Nervous	Mental disturbances; bizarre sensations; apprehension; fear of impending spasm or of being left alone. True tetany with tonic spasms—carpopedal, laryngeal, and occasionally general. Latent tetany with positive signs (Chvostek's, Trousseau's, Erb's). Paresthesias. Peripheral nerve hyperexcitability. Extremities frequently "go to sleep."
Special Sense	Tinnitus aurium. Alleged tendency to cataract formation.
LAB. FINDINGS	
Urine	Excessive elimination of lime (?)
Blood	Hypocalcemia—blood calcium from 6 to 8 mg. per 100 cc. (9-10 mg. normal range). Secondary anemia.
Metabolism	Deranged acid-base equilibrium; abnormal calcium metabolism. Reduced CH tolerance. Usually loss of appetite, loss of weight, and constipation.

Parathyroid Hyperfunction—Hyperparathyroidism

ENDOCRINE FINDINGS	Parathyroid hypertrophy; parathyroid tumors. Hypercalcemia.
APPEARANCE	
Structure	Bone disease such as osteitis fibrosa, bone cysts.
CLINICAL DIAGNOSIS	
Circulatory	Arterial calcification (?)

Alimentary	Abdominal pain. Occasional vomiting. Polydipsia.
Nervous	Muscular hypotonicity; pain in the bones.
LAB. FINDINGS	
Urine	Great increase in output of lime; evidences of glomerular irritation. Polyuria frequent.
Blood	Blood calcium increased from 12 to 20 mg. per 100 cc. Hypohepatism. Anemia.
X-Ray	Bone rarefaction with greatly reduced bone shadows (localized); spontaneous fractures.

THE PANCREAS

Diabetes Mellitus (Hypopancreatism)

ENDOCRINE FINDINGS	Pancreatic insufficiency (digestive as well as endocrine), hepatic detoxicative deficiency, adrenal irritability (sensitive to epinephrine).
APPEARANCE	
Skin	Dry skin; pruritus. Susceptibility to furunculosis, carbuncles, etc.
Structure	Rheumatic muscular pains and cramps; protracted lumbar pain.
CLINICAL DIAGNOSIS	
Circulatory	Arteriosclerosis with intermittent claudication; diabetic gangrene.
Alimentary	Hypocholia; clay stools. Increased hunger and thirst. Rapid dental caries; pyorrhea with loss of teeth.
Respiratory	Air hunger (due to acidosis). Fruity odor of breath (acetonemia). Susceptibility to pulmonary tuberculosis.
Nervous	Myasthenia. Tendency to neuralgia. Neuritis with anesthesias, paresthesias, loss of reflexes, and trophic disturbances. Diabetic coma.
Urogenital	Polyuria, nocturia, glycosuria (ketonuria). Libido and potentia decreased later.
Special Sense	Early cataract.
LAB. FINDINGS	
Urine	Glycosuria, increased density, acetonuria, hyperacidity.
Blood	Hyperglycemia. Anemia.
Metabolism	Reduced CH tolerance. Defective fat metabolism with lipemia, ketonuria, and acidosis. Basal metabolic rate may be increased. Emaciation often marked (*diabète maigre*).

THE THYMUS

Persistent Thymus—Hyperthymism

ENDOCRINE FINDINGS	Status thymicolymphaticus; enlarged thymus (X-ray). Hypoplasia of chromaffin system. In infants, an enlarged thymus demonstrable on physical examination may be shown also by the X-ray and vice versa.
APPEARANCE	
Skin	Parchment-like pallor of skin. Infiltration of subcutaneous fat. Heterosexual distribution of hair.
Structure	Anomalies of skull; heterosexual physical configuration (*typus femininus* in males and *typus masculinus* in females). Delayed epiphyseal closure. Muscular system relaxed and poorly developed. Osseous system fragile.
CLINICAL FINDINGS	
Circulatory	Congenital hypoplasia of cardiovascular system. Palpitation; dyspnea; cyanosis; sudden death. Very susceptible to infections, especially of the upper respiratory tract. A weakling in person and behavior.
Alimentary	Enlarged upper incisors; disproportion between median and lateral incisors.
Respiratory	Asthma. Asphyxial paroxysms. Thymic stridor.
Nervous	Asthenia; fatigability.
Urogenital	Hypoplastic genitalia; cryptorchidism.
LAB. FINDINGS	
Blood	Marked lymphocytosis; lymphatic hyperplasia.
Metabolism	Rapid changes in body weight. Temperature varies. It is now quite generally believed that an early involution of the thymus is accompanied by premature puberty and that a persistent thymus, or failure to involute, is accompanied by delayed puberty. In other words, there is a reciprocal relation between the thymus and the gonads.

28. A SYNOPSIS OF ENDOCRINE SYMPTOMATOLOGY

(After that of Prof. Nicola Pende, of Genoa)

THE THYROID GLAND

Athyroidia Totalis

Thyroid absent or sclero-atrophic.

Skin diffuse, myxedematous, infiltration of pale yellowish color, dry, furrowed, squamous, cold, senile. Sunken, atonic, drowsy-looking eyes. Hair, eyebrows, body hair sparse or slowly falling, opaque, dry. Nails atrophic, fragile. Teeth deciduous, carious.

Muscles flaccid, sclero-atrophic. Bones atrophied, sclerotic, fragile.

Genitalia atrophied only in advanced cases. In women, amenorrhea or menorrhagia; impregnation possible. In men, anaphrodisia, impotence.

Psychic, psychomotive, and psychosensorial reactions slow. Deep torpor, ideational, mnemonic, volitional, emotive deficiency. Tendency to hallucinations, depressive psychosis, and somnolence; speech slow, monotonous.

Cachectic condition masked by myxedematous infiltrations.

Serious slackening of basal metabolism and albumin combustion. High carbohydrate tolerance. Oliguria. Hypothermia, keen cryesthesia.

Slight anemia with low corpuscular value; mononucleosis, eosinophilia. Lowering of the autonomous tone, principally of the sympathetic.

Bradycardia, microsphygmia. Absence of sudor. Marked intestinal atony.

When occurring in periods of growth: Arrest of skeletal development, chiefly in the length of bones, hence trunk is thick-set; bones tubular, short, stumpy. Arrest of dental, cranial, facial, genital, and intellectual development. Deficiencies in hearing and speech. Infantile balloon-like body.

Partial Hypothyroidism

Thyroid frequently very large—struma. Often palpebral edema, maximal in the morning.

Hair sparse, located high on the forehead and temples; usually dry and brittle. Absence or sparseness of hair on the outer third of the eyebrows; scorched appearance of eyebrows. Nails short or atrophic, either streaked or with whitish spots. Caries, or spontaneous, premature falling-out of the teeth. Scanty perspiration.

Tendency to myalgia, arthralgia, sclerosis of the articular and periarticular tissues.

Amenorrhea, leukorrhea, dysmenorrhea, menorrhagia; diminution of sexual appetite, but not constant. Frequent delay of puberal crisis, incomplete sexual development (uterus infantile; cryptorchidism). In some women,

scanty lactic secretion. Apathy, a constant feeling of cerebral and muscular fatigue; phlegmatic temperament. Diurnal somnolence. Habitual headache.

Frequent obesity of moderate degree, often with accumulations of soft fat (pseudolipomas) in the supraclavicular fossæ, at the root of the tongue, around the breasts, and in the dorsal cervical region; padding on dorsum of hands, cuffing about wrists and ankles.

Tendency to slowing down of nutritional metabolism. Sugar and carbohydrate hunger.

Urine rather scanty, not very acid nor alkaline, frequently albuminuric and oxaluric. Extreme sensitiveness to cold, extremities often cold and cyanotic, tendency to chilblains and edema of the distal parts. Bradycardia, clinostatic bradycardia, arterial pressure variable—may be high or low. Tendency to premature atheroma. Excessive development of the venous and lymphatic systems. Torpor of vascular reactions.

Anorexia. Habitual constipation. High degree of tolerance for iodine preparations.

MORBID HYPERTHYROIDISM

Thyroid hyperplastic, richly vascularized or pulsating, sensitive.

Skin thin, glossy, warm, easily flushed and perspiring quickly, juvenile appearance, frequently with spots of brown pigment. Protruding eyes, with full rima palpebrarum, brilliant, with expressive looks. Not infrequently, circumscribed, acute, cutaneous edema. Rapid canities and calvities, generally circumscribed. Muscular atony and asthenia. Diffuse tumors. Bones thin, growth rapid in length. Tendency to periodic hydrarthrosis.

Genital atrophy. Mammary hypertrophy in males; atrophy in females. Diminution of sexual appetite. Impotence. Amenorrhea.

Excessive emotivity, hyperexcitability and psychic instability, cerebral restlessness. Continual need of motion. Insomnia.

Tendency to hallucinatory conditions, mania, melancholia, and hemicranial attacks.

Increase of oxidative processes, of albumin metabolism; loss of phosphorus and lime. Reduced carbohydrate tolerance. Marked and progressive emaciation, sometimes disappearance of fat from upper parts of body.

Extensive variations in metabolism. Nervous or alimentary glycosuria.

Tendency to hyperthermia; sometimes neurotic fever. Excessive sensation of heat. Acroerythrosis; extremities frequently hot, flushed, and perspiring.

Leukopenia with corresponding lymphocytosis.

Tachycardia with great instability of the pulse. Vascular erethism, with prevalence of vasodilatatory phenomena. Hyperidrosis.

Appetite good, often capricious. Variation of gastro-intestinal secretory tonus; attacks of salivation, hyperchlorhydria, vomiting, diarrhea, muco-membranous enteritis.

Great instability of the tonus of the vegetative nervous system.

When occurring before puberty, skeletal development is accelerated in the direction of height, with premature uniting of the epiphyses; persistent juvenilism of form and habitus.

CONSTITUTIONAL HYPERTHYROIDISM

Thyroid slightly increased in size, or even of normal volume.

In Infants: Scarcity of fat; hair plentiful, lustrous, with no tendency of the scalp to parasitism or eczema. Sexual physiognomic traits prematurely pronounced. Genitals prematurely developed. Eyes bright and intelligent.

Sleep scanty. Lymphatic glands undeveloped (?)

Rapid ossification of the fontanelles. Premature or rapid development of the teeth, regularity in conformation, rarity of caries.

Premature development of speech, ambulation, and intelligence. Great vivacity and restlessness. Tendency to diarrhea.

In Adolescents: Very rapid increase in height and tendency to longilinear figure. Rather retarded development of the musculature. Rapidly occurring muscular fatigue. Tendency to the scoliosis of adolescence.

Premature development of the sexual instinct and sex characteristics; genital organs, however, usually not much developed. Frequent occurrence of psychic impotence and attacks of sexual frigidity.

Tendency to tachycardia and vasomotor neurosis. Susceptibility to bacillary infection (typhus, pulmonary tuberculosis).

In the Adult: Noticeable development of the pilary system, affecting mostly the hair of the head, eyebrows, and eyelashes. Margo supraciliaries rather prominent. Teeth excellently developed. Rapid growth of the nails.

Bodily sex characteristics strongly differentiated, but frequently with attacks of weakness and exhaustion. Bone development predominating in length, restricted in breadth.

Habitual leanness; fattening difficult. Muscular strength deficient, muscles slender. Rapid variations in the turgor of the tissues and in weight.

Persistent or prolonged juvenility of body and mind. Intelligence well-developed, quick, vivacious, with excessive development of the sense of criticism. Great emotivity and effectivity. Strong will-power, temperament later becoming changeable. Tendency to fits of depression and to pessimistic ideas. Classic neuro-asthenic characteristics.

Cardiac and vasomotor hyperexcitability, maximum in the vasomotors of

the head and hands. Reduced sensibility to cold. Hands almost always warm and moist; hyperidrosis, especially of the extremities and armpits.

Tendency to atonic phenomena of the stomach. Defecation frequent and stool usually of soft consistency. Increased sensibility to iodine preparations.

In women, intermittent fecundity; lactic secretion plentiful; frequently the upper lip is covered with down.

Number of red corpuscles and quantity of hemoglobin also above normal.

In Old Age: Disposition to senile tremor, Parkinson's syndrome, and attacks of cerebral congestion. In women, ready tendency to the appearance of symptoms of mild masculinism, and occasionally calvities of masculine type.

Hypertrichosis, hirsutism, hair coarse. In women, masculine arrangement of the hair. Teguments thick, not delicate like those of the constitutional hyperthyroid subject.

Genital function very active and premature.

Vascular hypertension. Disposition to vascular sclerosis, visceral sclerosis, and hyperplastic sclerosis of the nasopharyngeal, auditory, and laryngeal mucous membranes.

THE PITUITARY GLAND

TOTAL HYPOPITUITARISM

Narcolepsy and lethargic condition.

Slackening of the pulse and respiration.

Great insensibility to pain.

Notable fall in temperature and blood-pressure.

Rapid progressive cachexia.

PARTIAL HYPOPITUITARISM

General adiposity (except above clavicles and below elbows and knees), frequently rapid and of considerable proportions, with predilection of the fat for the regions of the pubis, mammæ, thighs, supraclavicular fossæ, and antero-inferior abdominal wall. (In adolescents, the fat distribution is often like that in female adults.) Sometimes, especially in adults, there are circumscribed lipomatous masses (hands, feet).

Partial or complete inhibition of sexual functions, with hypogenesis or retrogression of the genitals.

In Infants: Deficient stature with excessive adiposity. Defective development, both of trunk and limbs, also in length and thickness of the bones. Irregular dentition, very small mandible, mouth narrow and circular in form.

Eyes either too close together or too far apart, orbits almost round, eye-

brows sparse. Frequently the nose is rather small and nasal respiration difficult; adenoid growths in the nasopharynx. External genitals hypoplastic.

In Adolescents: Persistence of the puerile or feminine type of skeleton, recognizable by the delicate face, small hands with delicate tapering fingers, breadth of the pelvis, and pronounced lumbar lordosis.

Skin and cutaneous appendices of female type; skin delicate and transparent, only slightly tinted; nails delicate and pointed with only slightly developed lunulæ; hair silky—that of armpits and pubis fine and of feminine arrangement.

Teeth frequently irregular and superimposed in the mandible by reason of the restricted alveolar margins; canines sometimes of the same shape as the incisors.

High carbohydrate tolerance. Sugar hunger. Hematic lymphocytosis.

Subnormal temperature. Slight hypotension. Slow pulse. Vagotonia. Muscular asthenia and very marked relaxation of the articular ligaments. Constipation.

Psychic apathy, somnolence, fits of distraction, hypoalgesia, loss of normal sense or great irritability and impulsiveness. Pituitary headache. In the milder forms, asthenic habitus and asthenia universalis.

MORBID HYPERPITUITARISM

Tendency to adiposity in advanced stages, or to cachexia.

Suppression of genital functions, sometimes premature, sometimes at the commencement; sexual hyperexcitability and increased size of the external genitals.

Gigantism in youths, with excessive growth of bones (including the head) both in length and in breadth. In adults, osseous growth principally in breadth, most pronounced in face, hands, and feet (acromegaly). Tendency to circumscribed hyperostosis.

Hyperplasia of the connective tissues. Hypertrophy of the epidermis, cutaneous appendices, derm, and subcutis; hence skin thick and dense, not very mobile or transparent. Hair coarse; nails hypertrophic. Not infrequently universal hypertrichosis; in women, masculine hypertrichosis.

Polyuria and glycosuria frequent, but also frequently normal or subnormal carbohydrate tolerance.

Hematic lymphocytosis with eosinophilia.

Hypotension, more rarely hypertension.

Muscular asthenia. Apathy and somnolence, rarely restlessness. Painful acroparesthesia.

In tumor cases, sella turcica increased and deformed.

THE ADRENAL GLANDS

TOTAL HYPOADRENIA

Intense diffuse melanoderma of the skin and of the mucous membranes, especially the tongue.

Severe muscular adynamia. Cachexia.

Severe intellectual asthenia, incapacity for any mental work whatever; fits of psychic irritability or of melancholic depression.

Notable reduction of blood-pressure and severe cardiac atony. Hypothermia.

Coma-vigil. Tendency to sudden death.

PARTIAL HYPOADRENIA

Slight melanoderma of parts most exposed to the light and to lesions, or only scattered cutaneous spots.

Myasthenia. Disposition to Erb-Goldflam myasthenia.

Cardiovascular hypotension.

Status lymphaticus and hematic lymphocytosis.

In juveniles, habitus tending to long, slender, tubular bones; slight retardation and incompleteness of sexual development.

In pregnancy, disposition to intractable vomiting and eclampsia.

MORBID HYPERADRENIA

In Fetal Life: Syndromes of external feminine pseudohermaphrodism.

In Childhood: Symptoms of pubertas præcox with macrosomia præcox; notable development of the muscles, but proportions infantile.

In Adolescents (and beyond arrest of genital functions): Hypertrichosis of masculine type, the female sex almost always being affected. Exaggeration of male characteristics at the expense of female, especially in hyperadrenia due to tumors of the cortex.

In the Adult: Some primitive hypertonic conditions of the arteries, with cardiac hypertrophy; certain early forms of arterial atheroma; transitory nervous glycosurias. Sexual development in women frequently accompanied by virilism; frequently by obesity.

CONSTITUTIONAL HYPERADRENIA

Athletic and hypertensive constitution. In women, slight hypertrichosis of masculine type. In the period of growth, macrosomia with early sexual and intellectual development, adiposity, psychic hyperexcitability, notable muscular strength, hypertrichosis (simple hyperfunction of the adrenal cortex, not due to hypernephroma).

THE PARATHYROIDS

TOTAL INSUFFICIENCY

Acute incurable tetany (except by replacement therapy).

Tremors and epileptoid seizures. Sphincteral spasms.

Cachexia. Acidosis.

Hyperexcitability and vasomotor instability. Paresthesia.

Attacks of acute, circumscribed cutaneous edema and of gastric, intestinal, and sudoral hypersecretion.

Acute dystrophy of the hair, teeth, and nails.

Reduced carbohydrate tolerance.

Intelligence preserved. Hallucinatory delirium.

PARTIAL INSUFFICIENCY

Chronic tetany, hyperexcitability of the motor nerves, mostly anodal. Mechanical hyperexcitability of the muscles.

Tendency to myotonic, choreiform, epileptiform phenomena; phenomena of psychic exaltation, hallucinations, delirium, acroparesthesia.

Hyperexcitability of the vegetative nervous system, with alternating crises of sympathicotonia and vagotonia. Prevalence of phenomena of angiospasm and of hypertonia of the peripheral arteries. Face and extremities pallid and cold.

Laryngeal, gastric, and intestinal spasms.

Sudden appearance of gray hair and of acute alopecia—diffuse and circumscribed.

Dental disorders; fragility; defective development of the enamel.

Rapidly developing cataract. Underdevelopment and fragility of the skeleton, but without suspension of sexual development.

Angioneurotic cutaneous edema.

In women during pregnancy, childbirth, puerperium, and suckling, attacks of eclampsia and albuminuria.

Hematic mononucleosis.

THE GENITAL GLANDS—OVARIES, TESTES

TOTAL INSUFFICIENCY

In prepuberty, excessive growth in length of the lower limbs; legs and arms appear too long for body. Hypoplasia of trunk, head, and face; height rather above the average.

Absence of evolution of the genitals, pubic hair, voice, secondary sex characteristics; hair and teeth well developed. Skin delicate and poor in pigment.

Apathy and psychic feminilism in men. Intelligence and mentality usually normal.

In adults, tendency to regression of the genitals and the secondary sex characteristics.

Many fine wrinkles in skin, especially about face; skin yellowish and parchment-like.

Tendency to adiposity, most marked on the pubis, around the mammæ, and on the thighs.

In women, frequent phenomena of nervous hyperexcitability, particularly vasomotor.

PARTIAL INSUFFICIENCY

Scanty development of sex characteristics. In men, often female habitus; in women, indications of masculinism. Asexualism, frigidity.

In prepuberty, skeletal development somewhat excessive in direction of length, mostly excessive length of the lower limbs.

Adiposity (at times slight) most marked at the mons veneris, on the lower abdominal region, buttocks, breasts, upper eyelids. At other times, more diffuse and serious.

Hair plentiful. Skin pale and yellow, often prematurely wrinkled.

Muscles hypotrophic and hypotonic.

Apathy; intelligence preserved. Mental depression, patient often blue, nervous, and suspicious.

In women before periods, colds and sore throat; facial acne exaggerated; hands and feet "go to sleep" frequently. Occasionally a marked gain in weight occurs just prior to menses.

MORBID HYPERFUNCTION

In Infants: Sexual and somatic development accelerated and premature. Premature consolidation of the epiphyses, causing ultimate stature below the average.

In Adolescents: Premature ossification of the epiphyseal cartilages. Excessive development of genitals and sex characteristics, frequently also of the muscles.

Chlorosis(?)

Osteomalacia(?)

CONSTITUTIONAL HYPERFUNCTION

Sexual function very active, secondary sex characteristics very pronounced. In women, as also in men, the climacteric is rather delayed.

THE PANCREAS

TOTAL INSUFFICIENCY

Severe glycosuria, frequently with polyuria. Acetonuria.

Absolute intolerance of carbohydrates; persisting, moreover, during fasting. Steatorrhea.

Serious malassimilation and malnutrition.

Increased disassimilation of albumin and fats. Cachexia.

A form of infantilism due to hypopancreatism (B. Bramwell).

PARTIAL INSUFFICIENCY

Alimentary glycosuria, or slight chronic diabetes with adiposity. Excessive malassimilation of albumin, with no acetonuria. Normal intestinal absorption of albumin and fats.

THE THYMUS

TOTAL INSUFFICIENCY

In Infants: Severe athrepsia. Skeletal nanism, with thick, short, deformed, fragile bones. Serious types of idiocy.

PARTIAL INSUFFICIENCY

In Infants: Deficient development in the weight of the organism with normal or premature morphologic evolution.

Bones slender, fragile, poor in calcium. Muscles hypotrophic and hyposthenic.

Tendency to nervous hyperexcitability, rachitic manifestations, and muscular dystrophy.

MORBID HYPERFUNCTION

In Infants: Habitus plump, or even fat, with excessive nutrition. Facial complexion at times subcyanotic; at others, extremely pallid.

Attacks of asthma and laryngospasm.

Frequent hyperplasia of the lymphatic organs and of the spleen.

Remarkable dilatation of the left heart and arterial hypotonia.

Sudden death from occasional and very slight causes, as a fall, an anesthetic, etc.

In Adolescents and Adults: Habitus frequently longilinear with rather slender tubular bones; delayed ossification of the epiphyses; feminine configuration of the skeleton in males.

Difficulty in breathing; asthmatic tendency. Thymic asthma.

Suprapubic and axillary hypertrichosis; heterosexual location of hair and fat.

In women, frequently remarkable masculine development of the skeletal musculature.

Genital hypoplasia.

Skin pale and soft with a chlorotic tint. Dried out, wrinkled appearance of hands and face.

Pronounced cardiovascular hypotonia, tachycardia, with dilatation of the left heart. Strong tendency to fainting fits upon slight psychic causes. Occasionally hypoplasia of heart and arteries.

Secondary anemia usual. Pronounced lymphocytosis, frequent marked reduction of hemoglobin.

Intolerance to thymus preparations. Excessive sensitivity to pilocarpin.

Enlargement of the thymus observable by the X-ray and by percussion (thymic zone displaced in an upward direction by breathing or by raising the head in a backward direction).

THE PINEAL GLAND

TOTAL INSUFFICIENCY

In Infants: Macrogenitosomia præcox, frequently with obesity or heterosexual manifestations.

In Adults: Obesity or cachexia.

Calcification of the gland visible by X-ray at the age of 7 years.

PARTIAL INSUFFICIENCY

Pubertas præcox.

Hypotrophy and muscular asthenia(?)

Obesity(?)

29. A CLINICOPATHOLOGIC CLASSIFICATION OF THE UNIGLANDULAR DYSCRINISMS

(After that of Prof. Nicola Pende, of Genoa)

I. THYROID

ATHYROIDISM	Complete myxedema in adults; Bourneville's myxedematous idiocy in growing subjects.
HYPOTHYROIDISM	Incomplete myxedema in adults, incomplete infantile myxidiocy, myxedematous infantilism, paroxysmal hypothyroidism, minimal hypothyroidism, monosymptomatic hypothyroidism.
HYPERTHYROIDISM	
Hormonic (*orthoplastic*)	Hyperthyroid temperament; attacks of puberal and menstrual physiologic hyperthyroidism; transitory emotive hyperthyroidism.
Dyshormonic (*metaplastic*)	Classic Basedow syndrome, Basedow-like syndromes, variable or paradoxic partial hyperthyroidism. (Léopold-Lévi's "thyroid instability.")

II. PITUITARY

APITUITARISM	Cachexia hypophyseopriva. Pathologic lethargy.
HYPOPITUITARISM	Adiposogenital dystrophy—Fröhlich type. Pituitary nanism and pituitary infantilism. Pituitary feminilism.
HYPERPITUITARISM	
Hormonic (*orthoplastic*)	Hyperpituitary temperament. Slight eurythmic physiologic gigantism. Transitory physiologic hyperpituitarism of puberty and pregnancy.
Dyshormonic (*metaplastic*)	Acromegaly, pituitary gigantism, and acromegalo-gigantism.

III. ADRENALS

ANADRENIA	Acute anadrenia (asuprarenalism) of the following forms: Sudden death, choleric, apoplectic, pseudoperitonitic, myocardiac, encephalitic.
HYPOADRENIA	Addison's syndrome. Ferrannini's constitutional chronic angiohypotonia. Tuberculosis of the adrenals, periodic asthenia, hypoadrenia of pregnancy, etc.
HYPERADRENIA	
Hormonic (*orthoplastic cortic.*)	Athletic and hypertonic constitution.
Dyshormonic (*metaplastic medull.*)	Pseudohermaphrodism of adrenal origin. Transitory glycosuria of adrenal origin. Forms of adrenal arterionecrosis.

IV. PARATHYROIDS

APARATHYROIDISM	Severe spontaneous tetany, severe post-operative tetany.
HYPOPARATHYROIDISM	Slight or latent tetany, spasmophilia in infants and adults.

V. GONADS

AGONADISM	Syndrome of early castration. Syndrome of delayed castration.
HYPOGONADISM	Eunuchoidism of gerodermic form; feminilism of eunuchoid form; delayed hypogenitalism. Virilism of ovarian origin. Obesity of genital origin.
HYPERGONADISM	
Hormonic (*orthoplastic*)	Hypergenital temperament. Eurythmic pubertas præcox. Hypergenital nanism.
Dyshormonic (*metaplastic*)	Pubertas præcox of primary genital origin, with heterosexual symptoms. Chlorosis (?)

VI. PANCREAS

APANCREATISM	Severe lean diabetes.
HYPOPANCREATISM	Slight fatty diabetes. Alimentary glycosuria. Pancreatic obesity.

VII. THYMUS

ATHYMISM	Severe congenital idiocy (?)
HYPOTHYMISM	Pedatrophia with atrophy and softness of the bones and muscular atrophy (?)
HYPERTHYMISM	
Hormonic (*orthoplastic*)	Infantile macrosomia (?)
Dyshormonic (*metaplastic*)	Status thymicus in children and adults.

VIII. PINEAL

APINEALISM	Macrogenitosomia præcox of pineal origin. Pineal cachexia.
HYPOPINEALISM	Puberal precocity. Pineal obesity. Muscular asthenia and hypotrophy in young girls (?)

30. A CLASSIFICATION OF THE PITUITARY SYNDROMES
(After those of Dr. William Engelbach, of New York)

THE CONSIDERATION of the symptomatology of pituitary dysfunction is peculiarly complex for a number of reasons:

1. The pituitary has several different structures, each capable of producing several hormones.

2. Since these hormones regulate growth and sexual development, the time of the interference with the pituitary function makes a great deal of difference; and it is necessary to separate prepuberal upsets from those occurring after maturity.

3. The anatomical situation of the pituitary in the sella turcica at the base of the brain is such that any slight enlargement of the gland may cause pressure with headache and other symptoms, depending upon the degree of pressure. If there is actually a new growth in the pituitary tissue, a whole train of "neighborhood symptoms" is produced, which lessens the simplicity of the diagnosis. Besides this, the pressure on the pituitary itself obviously must interfere with its physiology.

4. The pituitary is peculiarly intimate with several other glands; hence, in well-defined pituitary dysfunction, and certainly in ultimate pituitary disease, there are compensatory reactions elsewhere in the endocrine system that make it difficult to attribute all the symptoms to the actual pituitary disorder.

5. Finally, dyspituitarism is not a hard and fast condition that never changes. The conditions that irritate or damage both lobes may cause hypofunction or hyperfunction; but a functional hypopituitarism may be fairly well compensated and conditions changed correspondingly, while marked degrees of hyperfunction are followed by depletion, atrophy, and real hypopituitarism (the "post-hyperpituitaric hypopituitarism") in which opposite symptoms replace those previously noted. It is all most disconcerting to any save the superspecialist.

Another complicating factor has to do with the balance between the pituitary functions themselves. It is not yet positively known whether certain symptoms are caused by deficient or excessive secretion. For instance, polyuria is found with evidences of both hypofunction and hyperfunction of the posterior lobe. In fact, H. Bab, of Germany, has had to concoct a theory to explain this; namely, that polyuria is caused by a defect located in the pars intermedia.

However, in the classification that I have prepared from Engelbach's tables in Tice's "Practice of Medicine," Cecil's "Text-Book of Medicine," and

several articles by Engelbach and other writers, the essential pituitary findings are given, with the outstanding peculiarities italicized. The reader must remember that these diagnostic pictures are often obscured by reactions in associated glands. Indeed, it cannot be demonstrated that each and every symptom is purely and simply of pituitary origin. In fact, in the consideration of dyspituitarism from a therapeutic standpoint (83), there is plenty of authentic evidence to confirm the customary pluriglandular aspects of pituitary disease.

I. PITUITARY—ANTERIOR LOBE

A. HYPOACTIVITY†

1. *Preadolescent:*

(Objective Signs)

Defective growth of all bones—*Diminutivism* (Lorain-Lévi type).

Short stature, upper measurement (*i.e.*, top of head to symphysis) greater than lower (*i.e.*, symphysis to soles). Span less than height. Small extremities. Acromicria, hand at least a third smaller than usual, with fingers always short, narrow, and tapering.

Upper teeth often quite large.

Sex glands hypoplastic or atrophic, absent secondary sex characteristics—*infantilism*. No hair on body (mons, axillæ, etc.). Pelvis broad (in male). Genu valgum.

(Subjective Symptoms)

Muscle tone and development normal.

Mentality usually good.

Sterility and absence of libido; impotence.

Temperature subnormal; pulse slow; hypotension usual.

B.M.R. and sugar tolerance normal.

Glycosuria and hyperglycemia absent.

Small sella turcica (except with tumor).

2. *Postadolescent:*

(Objective Signs)

Defective growth, except of long bones.

Normal or increased stature, variations as above.

Extremities and hands small, fingers as above.

† Both ultimates of dyspituitarism may be associated with pituitary tumor, *i.e.*, the neoplastic or aneoplastic types. Hence such classifications as "preadolescent aneoplastic hypopituitarism," etc.

Upper teeth large and occasionally widely spaced.
Hair distribution often usual.
Genital development normal; *gonad dysfunction* usually marked —amenorrhea, dysmenorrhea, loss of libido, impotence, etc.
Later genital atrophy.
Secondary sex defects not so marked.
Pelvis broad (in male). Genu valgum.
(Subjective Symptoms)
Muscle development normal but with gradual tendency to marked fatigability.
Average mentality.
Sterility and impotence.
Temperature subnormal. Pulse slow. Hypotension usual.
B.M.R. and sugar tolerance normal.
Responds to anterior lobe therapy. No posterior lobe signs as below.
Small sella turcica (except with tumor).

B. HYPERACTIVITY†

1. *Preadolescent:*

(Objective Signs)
Gigantism without posterior lobe signs.
(1) Normal, (2) eunuchoid, or (3) acromegalic giant. In (1) upper=lower, span=height; in (2) upper less than lower, span greater than height; in (3) upper greater than lower, span less than height.
Erect. Extremities large and prominent, acromegaly, hand a third larger than normal but properly proportioned. Wide, large fingers often with exostoses near joints. Bones long and slender.
Upper incisor teeth large and separated. Head large. In (3) prognathism.
Large, well-developed gonads.
Hypertrichosis, especially on body.
Pelvis narrow (in female). Genu varum.
(Subjective Symptoms)
Muscles large and overdeveloped; muscle tonus gradually lost quite early.
Normal sex activity. Menstruation often normal. Secondary sex characteristics well developed.

Temperament gradually changes, patient becoming indifferent and apathetic.

Pulse, temperature, and blood-pressure normal.

Normal sella turcica except with tumor.

2. *Postadolescent:*

(Objective Signs)

Acromegaly without posterior lobe signs.

Short and stocky. Stooped. Torso longer than extremities. Extra large feet and hands, "spade hand," club fingers; bones short and thick with wide tuberosities and exostoses. Head large, maxilla prominent. Prognathism.

Separation of upper incisors constant; lower teeth frequently separated also.

Large, well-developed gonads.

Hypertrichosis especially on chest and extremities; of masculine type in women.

Pelvis narrow (in female). Genu varum.

(Subjective Symptoms)

Muscles well developed; muscle tonus often retained unusually long.

Sex activity normal or even increased. Secondary sex characteristics well developed.

Of variable temperament, talkative. Bright mentality, but unstable in nature.

Pulse, temperature, and blood-pressure normal; sometimes moderate hypertension.

Normal sella turcica (except with tumor).

II. PITUITARY—POSTERIOR LOBE

A. HYPOACTIVITY

1. Pars intermedia (?)

Polyuria. Reaction to liquor pituitarii. No signs of anterior lobe or pars nervosa disorder.

2. Pars nervosa.

Pituitary obesity (girdle, mons, and mammary). Normal or slightly reduced B.M.R. Increased CH tolerance. No polyuria. Hyperglycemia and anterior signs absent. Tendency to intestinal atony. Tendency to somnolence (hibernation). Mental dullness and apathy. Temperature subnormal. Pulse slow.

B. HYPERACTIVITY

Pituitary glycosuria. Normal or slightly increased B.M.R., decreased sugar tolerance. Tendency to emaciation. Polyuria and anterior lobe signs absent. Intestinal spasticity. Nervous and mental instability. Temperature normal. Pulse often rapid.

III. BILOBAR PITUITARY DISEASE

A. HYPOACTIVITY

Fröhlich's disease with or without polyuria.

B. HYPERACTIVITY

Gigantism or *acromegaly* with increased B.M.R. and decreased sugar tolerance. No adiposity. Polyuria unusual.

C. HETEROACTIVITY

1. Anterior lobe hyper and posterior lobe hypo.
   Gigantism or acromegaly with polyuria.
2. Anterior lobe hypo and posterior lobe hyper.
   Genital aplasia, nanism, amenorrhea, etc., with pituitary *glycosuria.* Increased B.M.R.; decreased sugar tolerance.

31. ENDOCRINE DIAGNOSTIC TESTS

PRESENT-DAY STUDENTS of clinical endocrinology are fortunate in being able to follow many careful workers who have illuminated the diagnostic pathway with an extensive experience.

Certain tests and signs have been recorded which, though by no means always infallible indicators, serve to supplement the ideas that we may be building into a diagnosis.

The reader must not get the impression that this or that test is a sure guide to a diagnosis in a given instance. The following measures *added to other diagnostic procedures* help to confirm our diagnosis. It cannot be too strongly emphasized that a positive test for glycosuria or an increase in the B.M.R. does not prove that a patient has diabetes or hyperthyroidism. As a matter of fact, glycosuria occurs in dyspituitarism also, and the basal metabolic rate may be increased by factors quite outside the thyroid.

1. THE THYROID

The thyroid is one of the most important glands in the body, and consequently may be disturbed more frequently than any of the others. Since the thyroid is the chief chemical regulator, it manifests its irregularities. in disturbances of metabolism. Consequently, an accurate measure of the basal metabolic rate is invaluable as a differential diagnostic measure and a very accurate indicator of the thyroid function. But too often the B.M.R. is not absolutely a basal figure and hence the impression gained from it is not entirely dependable (67).

BASAL METABOLISM—There are a number of satisfactory machines on the market for making this necessary test. The method most frequently used is the gasometric. Since oxygen is absolutely essential to body chemistry, the measure of the oxygen intake over a definite period of time gives us an index of the chemical processes that are going on within the body. In order to get a correct estimation of the basal chemistry, or that amount of oxidation which is required in order to meet the body's minimal needs without any extra call upon them, it is necessary that the patient be *absolutely at rest,* that there be *no food in the stomach,* and *no mental excitement.* Consequently, it is preferable to make the test in the morning before breakfast while the patient is still in bed. Unfortunately, this is not often convenient, and so the figures are not a true indication of the *basal* rate. It is quite useless to make a basal metabolism test in a nervous patient. The B.M.R. is rarely correctly estimated in children.

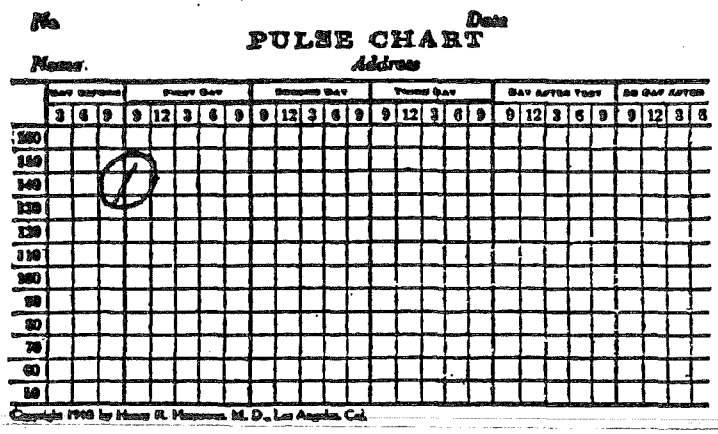
Full directions for using the different machines may be obtained from the manufacturers. Tables are supplied whereby the patient's height and weight may be converted into body surface and given the proper evaluation in the reading. After the mathematics of the test is carried out, the end-result is expressed in a *plus* or a *minus* figure. Zero has been used as an arbitrary starting point. Because there are some variations in all normal individuals, a leeway consisting of the difference between a *plus 10* and a *minus 10* is granted for these normals. The determination of the B.M.R. is a valuable aid in the diagnosis of variations in thyroid function. It is interesting to check this figure by Read's formula mentioned farther on.

HARROWER'S THYROID FUNCTION TEST—A patient's reaction to organotherapy is often an indication of the condition of the endocrine gland for which treatment is being administered. A sensitive gland is likely to react more quickly to organotherapy than an apathetic one. This is particularly true of the thyroid. The administration of thyroid extract to patients whose condition has been incorrectly diagnosed sometimes causes nervousness, irritability, and tachycardia.

To help to avoid unsatisfactory clinical experiences of this kind, I devised a simple method of testing thyroid function (*New York Med. Rec.*, Aug. 3, 1918, xciv, p. 196). It consists of giving definite, increasing doses of thyroid extract with a suitable inert excipient in a uniform, routine manner, and carefully studying the pulse and any symptoms that occur. The information thus obtained virtually gives us a differential diagnosis of goitre.

Considered from the standpoint of secretion, there are two distinct varieties of goitre: (1) the simple enlargement of the thyroid, which appears to be produced by the effort of the gland to supply an increased demand for its secretion; and (2) the hypertrophy that is due to some extra-glandular cause, such as toxemia or irritation. Simple goitre is caused by an attempt on the part of the thyroid to give the best service possible under the circumstances. It usually is benefited by a course of treatment including thyroid, iodine, etc., which tend to supply the need, thus rendering enlargement of the gland unnecessary. The goitre in the second class is commonly caused by (1) the toxins absorbed from foci of infection; (2) emotional disturbance; (3) deranged function of some other endocrine gland. The responsiveness to thyroid therapy differs according to the origin of the hypertrophy. In fact, that which is most beneficial in simple goitre is most detrimental in the goitre of hyperthyroidism. This thyroid test enables one to identify the early functional stages of thyroid sensitivity and to differentiate between latent hypothyroidism and hyperthyroidism.

The material for the thyroid function test consists of four doses each of ½, 1, and 2 gr. of the standard thyroid extract in graduated capsules and a chart similar to the one illustrated in Figure 1, to which is attached the following printed instructions:

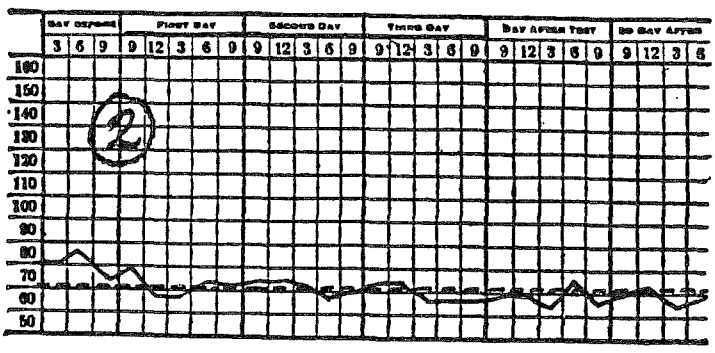


Instructions for Using the Test—"The pulse is counted and recorded at the consultation. The patient repeats this procedure at 6 o'clock and again at 9. On the following day, he takes the four *small* capsules with a swallow of water at 8, 10, 12, and 2 o'clock, recording the pulse five times during the day—at 9, 12, 3, 6, and 9 o'clock. The four *medium*-sized capsules are taken on the second day, and the *large* ones on the third day, the pulse being recorded under as nearly identical conditions as possible each day and at the same hours.

"On the fourth day and on the morning of the fifth, the pulse is tabulated as before. The chart is then plotted, the physician is consulted, and the data are carefully studied.

"It is important to watch for symptoms of irritability (temperamental or nervous), twitchings of the eyelids, lips, fingers, etc., breathlessness, and other manifestations. If, on the second or third day, these symptoms are present and *prominent,* the remaining capsules should not be taken; *but the chart is completed,* and a statement of symptoms, giving time of onset and other related facts, is made on the reverse side.

"It is wise to take the pulse each day under as nearly uniform conditions as possible, preferably before eating, after a ten-minute rest, and while sitting. Mark the chart with a dot in the proper square at its approximate position."

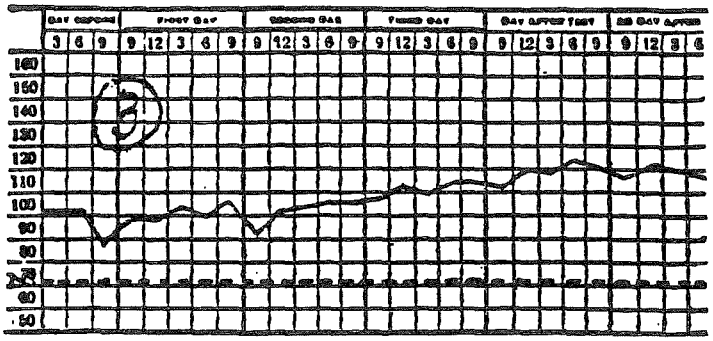


The Response to the Test—Patients' reactions to this routine administration of graduated doses of thyroid vary materially, depending upon the factor that one is attempting to discover. The thyroid substance produces little change from the normal pulse figure in apathetic hypothyroid cases.

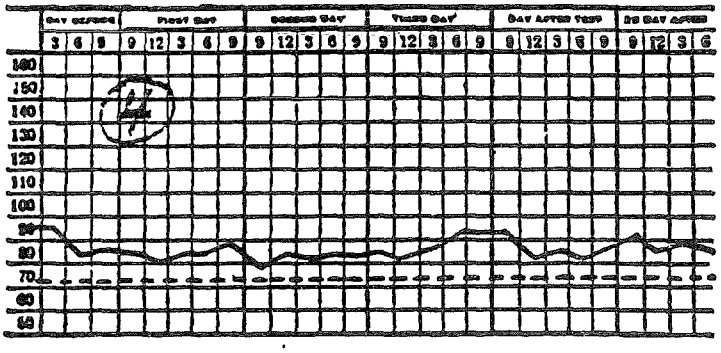
The reaction to the thyroid testing capsules in a case of moderate functional hypothyroidism is nicely illustrated on the chart above (Fig. 2). The

pulse is below normal and does not seem to be influenced at all, even by the heavy dosage of thyroid that is given on the third day.

The thyroid extract will temporarily stimulate the thyroid function of the normal individual. The pulse rate is also increased, but by the administered thyroid substance rather than by an excessive production of the thyroid hormone. Since these products are destroyed quite rapidly, the cardiostimulant action lasts only during the time of the greatest dosage of thyroid and *comes down to normal again on the following day.*

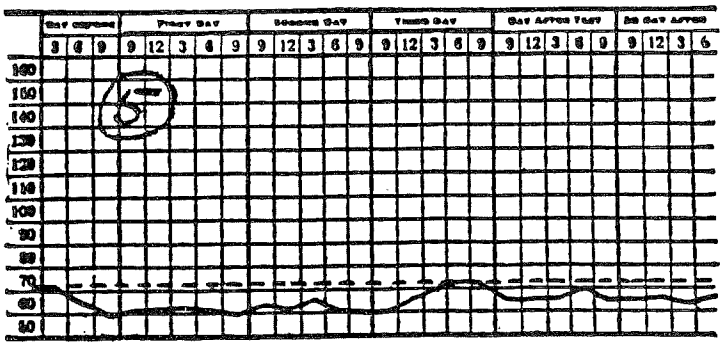


The pulse findings of various stages of thyroidism are characteristic: the greater the susceptibility, the wider the range. As will be seen in Figure 3, the average pulse rate is somewhat higher and more irregular than normal. Early in the administration of the thyroid, the pulse becomes more rapid until, at the height of the temporary gland feeding, it may reach well above any possible normal figure—100, 110, or even higher. Since this stimulus is not entirely from the administered product, but from the increased activity of the supersensitive gland, the pulse remains high for perhaps two days following the cessation of the medication. This is because the thyroid is working overtime, as is indicated on the chart. This test should not be used in well-defined hyperthyroidism with tachycardia; it is not necessary because the diagnosis should be clear without it. In latent cases in which there is an unexpected degree of thyroid sensitiveness, the routine advice suggests the omission of the last four capsules—the largest dose—but the continuation of the pulse record, with a note to this effect. Although the pulse findings will not be so exaggerated in a case of this kind, the indications are equally helpful.



The Discovery of Latent Thyroid Conditions — This test is more useful in the discovery of thyroid apathy or a latent thyroid sensitiveness than in the diagnosis of frank hyperthyroidism. Two out of many hundreds of cases that have been tested by this method presented charts that were quite unexpected and worthy of comment. The first was a patient with a highly

nervous temperament, staring eyes, fine tremor, sweating palms, and general sympathetic irritation. He was sent to me as a case of typical hyperthyroidism, yet some of the usual findings were missing, and the pulse was approximately normal. A thyroid function test was made and the preceding chart obtained (Fig. 4). Later an X-ray examination of the chest showed a subclavicular tumor of considerable dimensions. The sympathetic irritation was caused largely by the pressure of this intrathoracic tumor; the patient did not have the expected and typical features of hyperthyroidism after all.



Another patient of an opposite type had a large goitre that was about to be removed by surgery. About that time the physician heard of this test, tried it, and later sent me the accompanying chart (Fig. 5), from which it seemed clear that the patient had a well-defined degree of thyroid inactivity. Various other symptoms of Hertoghe's disease—*myxedème fruste*—were discovered, and the woman was given medication to stimulate the thyroid and ovarian functions. The goitre almost disappeared eventually, and the menstrual difficulties, which were quite prominent, were controlled simultaneously. In this case the thyroid function test saved an operation by giving broader information about the patient.

The Test in Chronic Disease—Still one other class of cases may benefit from the use of this test: I refer to chronic toxic and nutritional disturbances such as rheumatism, neurasthenia, tuberculosis, etc., in which elimination is very much below par and there seems to be a radical reduction in the oxidizing process. In such cases, a thyroid function test may indicate a marked degree of thyroid apathy and may direct attention to the possibility of stimulating this deficiency, with prospects of benefit from the obviously necessary thyroid therapy. It is true that many such cases may receive benefit from thyroid extract without the test, but there is greater satisfaction in having, when possible, a definite reason for each procedure.

The reference to tuberculosis calls for a word of explanation and caution: Many tuberculous persons have a well-defined thyro-adrenal insufficiency, which the thyroid function test clearly indicates, as do the blood-pressure and the urinalysis. This calls for obvious associated gland support. On the other hand, since the thyroid gland reacts to toxic stimuli, a latent degree of

hyperthyroidism may be identified easily by this test, in which case the indicated glandular treatment would be the opposite from that given to the tuberculous persons in the large class mentioned previously. A preparation containing pancreas, instead of a cell-stimulating thyroid combination, is recommended in these cases.

It has been said that this thyroid function test is nothing but the administration of thyroid extract and noting the patient's reaction; but unfortunately experiences of this kind are often failures, and our clearest recollections of them are the remarks about the uncomfortable feelings that the thyroid produced. This justifies the emphasis placed on this procedure, not merely in the differentiation of goitre as indicated, but in the search for scientific reasons for the use of thyroid extract as a part of the treatment in a given case.

GOETSCH'S EPINEPHRINE TEST—In 1918 Emil Goetsch, of Brooklyn, used the fact that patients suffering from hyperthyroidism are usually sensitive to injections of epinephrine, as a means of measuring thyroid irritability. The response depends upon the fact that thyroid hyperactivity irritates the sympathetic nervous system. The patient should be absolutely at rest, and should be assured that the test will not inconvenience him. Blood-pressure, pulse, and respiration records are made, then 0.5 cc. of a 1:1000 solution of epinephrine hydrochloride is given subcutaneously. The observations are continued at five-minute intervals. The test is considered positive if the systolic blood-pressure rises from 10 to 50 mm. of mercury in the first five minutes. The pulse rate is also increased at least twenty beats a minute. Usually the diastolic blood-pressure falls slightly. In half an hour there is another secondary rise, but to a smaller degree. The test is of value as an associate measure only; and, of course, it is of no value in hypothyroid conditions.

A slight modification of this test is advocated by L. Rogers, of Cardiff, Wales (*Lancet,* Nov. 10, 1928, ccxv, p. 970). The patient rests quietly in bed, and the pulse rate and systolic blood-pressure are taken at short intervals until they become constant and a mean is obtained. Then 0.5 cc. of adrenalin solution (1:1000) is injected subcutaneously over the deltoid, and a further series of readings is taken for fifteen minutes, while other signs and symptoms are being noted. Rogers used this procedure in a series of goitre cases and in a series of healthy volunteers. There was little or no response in the healthy subjects, while in all the goitre cases the symptoms were exaggerated. He concludes that the test (a) reveals the presence of incipient thyroidism; (b) provides a rough estimate of the degree of intoxication and of the extent of the reaction liable to follow operation; (c) shows

by absence of reaction that the goitre is not toxic and that there will be no post-operative reaction.

READ'S MATHEMATICAL RATIO—Some years ago, J. Marion Read, of San Francisco (*Jour. Am. Med. Assn.*, June 17, 1922, lxxviii, p. 1887), conceived the idea that a fairly close estimate of the B.M.R. could be based on the increased pulse rate and the pulse pressure of hyperthyroid patients. Increased heat production causes an increase in the flow of blood from the internal organs to the skin in order to facilitate the needed increase in the loss of heat through radiation. That this occurs is well known, and Read supposed that there must be a ratio between the increased flow of blood and the increased metabolism.

Based on this, a formula was worked out as follows: To 0.9 of the pulse pressure add the pulse rate and multiply by the factor 0.683; from the result, subtract 71.5; and the answer is the *approximate* B.M.R. This factor is quite close to the actual basic rate, but it is subject to error from other conditions that increase the pulse rate or raise the blood-pressure. Hence, these must be taken into consideration when making this mathematical test.

In discussing Read's method, David Metheny, of Seattle, Washington (*Northwest Med.*, March, 1931, xxx, p. 140), tells of having made sixty-seven comparisons between this formula and the actual B.M.R. He says:

"Like other observers, I found 40 per cent. of the cases gave an error of over 10 per cent. In the big majority of error cases, the formula gave a higher reading; in the remaining few, the formula as well as the basal metabolic test showed hyperthyroidism. At no time did the formula give a normal reading and the basal metabolic test show hyperthyroidism.

"My experience was too limited for final conclusions, but we must admit that we have received quickly and inexpensively a strong hint of the type of case before us. For example, if a patient had a blood-pressure of 90 over 120, we would have a pulse pressure of 30. Nine-tenths of this is 27, to which we add the pulse rate, say 80, giving us 107. Multiplying by 0.683, we get 73. Subtracting 71.5 from 73, we have a rate of essentially zero. Of course, we might know from other sources that such a patient does not have hyperthyroidism, but in spite of its obvious errors the formula has been a source of satisfaction to me."

BRAM'S QUININE TEST FOR HYPERTHYROIDISM—Another test, originated by Israel Bram, of Philadelphia, is based on the peculiar fact that a high tolerance to quinine is uniformly exhibited by patients suffering from thyroid intoxication. The patient is given a capsule containing 10 gr. of neutral quinine hydrobromide four times a day, with an abundance of lukewarm water. If hyperthyroidism does not exist, the patient shows symptoms of cinchonism after taking the third or fourth dose; patients with an idio-

syncrasy for quinine develop symptoms after the first or second dose; those who are naturally tolerant may not complain until after the sixth or even tenth dose. If hyperthyroidism is present, no symptoms develop even when the quinine is taken over a long period.

Bram states that there is a considerable percentage of error in B.M.R. and adrenalin tests, but the quinine test, when positive, differentiates hyperthyroidism from simple goitre, mechanical goitre heart, incipient tuberculosis, and several other conditions that may be mistaken for hyperthyroidism. It does not, however, distinguish between adenoma and Graves' disease. This test has the merit of great simplicity, and Bram, having employed it in more than three hundred cases, vouches for its clinical value.

KOTTMANN'S TEST—This photochemical blood-serum test for hyperthyroidism was introduced by K. Kottmann, a Swiss physician, in 1920. It depends on the rate of development of silver iodide in serum treated with potassium iodide and silver nitrate and exposed to strong light. Hyperthyroidism is said to delay the development. To 1 cc. of clear serum from the patient are added (1) 0.25 cc. of a 0.5 per cent. solution of KI and (2) 0.3 cc. of a 0.5 per cent. solution of $AgNO_3$. Silver iodide is formed, and the resulting suspension is exposed for five minutes to the rays of a 500-watt Mazda lamp at a distance of 25 cm. Then (3) 0.5 cc. of a 0.25 per cent. solution of hydroquinone is added, and the color changes are noted at intervals of five minutes. The silver iodide is reduced to silver and a brown color develops, the change being delayed in the presence of hyperthyroidism. It is well to run one or more controls with the suspected specimen.

W. F. Petersen *et al.* have tried this test in a large number of cases and conclude that it is of definite value, but that further study is needed in order to confirm its value in border-line cases. It is believed that the significance of the Kottmann test as a diagnostic of hyperthyroidism requires further critical study. For example, S. Morse and C. M. Fitch, of Columbus, Ohio, performed more than 195 tests by this method on known and suspected goitre patients, finding great variation in the results—a variation traced to the presence of CO_2 in the serum tested, which retards the reaction. This source of error is so pronounced that the authors think all work on the Kottmann reaction must be revised fundamentally from this standpoint. Several other writers, however, find the test simple and reliable, and it is suggested as of particular value in insane and neurasthenic patients.

EYE SIGNS IN HYPERTHYROIDISM—There are a number of signs on record that are sought for as of confirmatory value in exophthalmic goitre.

They are the result of the oculomuscular and sympatheticotonic conditions present in this disease:

Exophthalmos, or proptosis, is the first and basal sign of exophthalmic goitre. The eye itself seems to be pushed forward from its socket, and when it is closed without special muscular effort the lids do not fully cover the eye (lagophthalmos).

Dalrymple's Sign—In Graves' disease the sclera may show above or below the cornea—more markedly and frequently below than above. It may be absent above but present below, or vice versa. It is distinctly a sign to be observed in the eye at rest in its primary position.

Von Graefe's Sign—Lagging of the upper lid in relation to the upper edge of the cornea in motion from above downward. In health, if the eye is directed upward and then follows an object—say the finger—brought down *slowly* to the horizontal meridian, the relation of the upper lid to the cornea is constantly preserved; but, with the von Graefe phenomenon, the upper lid lags and, if there is sclera showing between the upper lid and the cornea in the position of rest, it is seen to be wider as the eye descends from above downward.

Wilder's Sign—Another eye sign due probably to sympathetic irritability in hyperthyroidism is that of W. H. Wilder. It consists of a peculiar little jerk or twitching of the eyes at the instant of changing the movement of abduction to that of adduction. This sign can best be elicited by having the patient gaze intently at the end of the finger or at a pencil held about 18 inches in front of the eyes and moved with a slow, even pace from side to side so as to make the eye perform an excursion of abduction and adduction. When the eye reaches the limit of the excursion and changes from abduction to adduction, there will be seen a more or less pronounced jerk or twitching before it regains its steady movement. Wilder says:

"I have observed this as one of the earliest signs, even before those of von Graefe, Stellwag, or Dalrymple, and I have never failed to get it in any case of exophthalmic goitre that I have studied. However, it may be observed in some nervous diseases, such as multiple sclerosis and lateral sclerosis, in which one may also observe varieties of spastic tremors of which this seems to be an illustration."

Möbius' Sign—Still one more ocular sign of hyperthyroidism is an inability to keep the eyeballs converged. This is not always found, but it is a supplementary test occasionally mentioned in the German literature.

2. THE PITUITARY

Although the basal metabolic rate may be somewhat decreased in hypopituitarism, that test alone cannot be used as an evidence of pituitary dysfunc-

tion. The clinical symptoms in pituitary disorders are most important. The distribution of fat, menstrual disorders, headache, and a tendency to lethargy must all be considered. Because the posterior lobe of the pituitary controls the carbohydrate metabolism, a test was devised on this basis, the value of which depends somewhat upon circumstances.

CARBOHYDRATE TOLERANCE TEST—Weigh the patient. Multiply this weight (in pounds) by 0.8; the result is the number of Grams of dextrose to be fed the patient in the morning, without breakfast. It is usually given in the form of lemonade. Test the urine for sugar at hourly intervals four or five times. If no sugar appears, *i.e.,* if there is an increased carbohydrate tolerance, the case is likely to be one of pituitary sluggishness, and pituitary therapy is in order. (Following pituitary feeding for some days, another test is likely to give a quite different response.)

Just as increased carbohydrate tolerance is suggestive of hypopituitarism, so a very low sugar tolerance is indicative of the opposite condition—hyperpituitarism—and not infrequently there may be hyperglycemia of moderate degree and the so-called "pituitary glycosuria." (Some recent writers insist that this test is not useful.)

PITUITRIN WATER-RETENTION TEST—It has been found by Oliver Kahm, of Detroit, that obese persons frequently show a definite tendency toward water retention, which is believed to be due to pituitary insufficiency. A therapeutic test for pituitary sensitiveness is easily made.

On arising in the morning, the patient empties the bladder and then drinks a quart of water on an empty stomach. No food or liquid is taken for four hours, and at the end of this time the bladder is emptied. All the urine passed during this period is collected and the amount compared with that secreted on another day under exactly similar conditions, save that 0.3 cc. of pituitrin (obstetrical) is injected intramuscularly at the time the water is taken. Normal persons, or those showing no pituitary insufficiency or sensitiveness to the extract, will secrete probably half as much urine when the pituitrin is given as without it. Apparently, the greater the pituitary sensitiveness, the less the amount of urine eliminated during the test. After the four-hour interval, it will be found that the initial increased water retention produced under the influence of the pituitrin is followed by a compensatory polyuria, which may continue for forty-eight hours.

SCHELLONG'S CIRCULATORY REACTION—F. Schellong, of Berlin (*Klin. Wchnschr.,* Jan. 17, 1931, x, p. 100), describes a peculiar circulatory disturbance in pituitary cachexia, which manifests itself in collapse and

fainting. Because the attacks of fainting followed even slight bodily exertion, the blood-pressure and heart action were tested during work. It was found that the blood-pressure of these patients was not, as in normal patients, increased during exertion. On the contrary, both systolic and diastolic pressures were decreased, and the heart action did not show any changes. That this disturbance is not dependent upon the height of the blood-pressure during rest was proved by the fact that, even when the blood-pressure was increased by an injection of epinephrine, a considerable decrease followed the exertion. As this defect in circulatory regulation can be counteracted, partially or wholly, by giving anterior lobe preparations, Schellong concludes that one of the pituitary hormones influences the peripheral vessels. The decrease in blood-pressure during bodily exertion in hypopituitary patients is probably a result of a reduction in the peripheral resistance or of the abnormal dilatation of the peripheral vessels.

OCULAR CHANGES—Because of its location at the base of the brain, a definite increase in the size of the pituitary gland may produce various eye symptoms. There may be bitemporal hemianopsia with the outer fields of vision impaired. This is most accurately demonstrated and charted by recourse to perimetry. In addition there may be ocular palsies or alterations in the color vision, which also can be measured.

SELLAR RADIOGRAPHY—An X-ray examination of the sella turcica, the bony cup that holds the pituitary, is more frequently of value in a negative than a positive way. It is very possible to be misled in reading an X-ray picture if the position in which that picture is taken is not definitely known.† In other words, what is known as a lateral radiograph may vary considerably depending upon the operator. The standard measurements are: anteroposterior (horizontal), from 14 to 15 mm.; vertical, from 9 to 10 mm. An arbitrary figure is impossible, since the size of the pituitary fossa varies with the size of the skull. The size of the sella is not really so important—it is only one of the clinical findings. The presence of a small, irregular, or bridged sella may explain pituitary pressure. On the other hand, a large, open sella with well-divided clinoids, which apparently would allow sufficient freedom to the pituitary gland, may still enclose a pituitary sufficiently congested to cause pressure symptoms. I believe in making my own sellar reading, always considering the findings in conjunction with the patient's clinical symptoms.

†My friend, Dr. D. M. Ghrist, of Glendale, Calif., has devised an ingenious apparatus by means of which a known, predetermined, and recorded position of the head is possible. It is of value in all head and sinus X-ray work, especially where comparisons are desirable.

3. THE ADRENALS

BLOOD-PRESSURE—A study of the arterial tension over a short period and under varying circumstances is an excellent guide to adrenal function, for the cardiovascular tone, including that of the heart muscle itself as well as that of the vessel walls, is dependent largely upon adrenal factors for its maintenance. Hypoadrenia ordinarily spells hypotension.

HYPOSPHYXIA—The circulatory syndrome to which the late Prof. Alfred Martinet, of Paris (*Presse méd.*, 1913, xxi, p. 635), gave this name is perhaps the most easily determinable of all the tests for hypoadrenia. This picture is the result of a modified form of circulatory asphyxia; hence the name. The stimuli that regulate the circulation, cardiac efficiency, and blood-pressure are deficient; consequently, a study of the manifestations of circulatory tone leads to valuable information. Poor circulation, with bluish and cold extremities, myocardial asthenia, reduced blood-pressure (both the systolic and pulse pressure), and other evidences of asthenia due to poor circulation, are commonly associated with adrenal insufficiency. Confirmation of this assumption follows the control of part or all of these hyposphyxial symptoms by adrenal therapy. It is quite common for patients with the functional adrenal insufficiency that so commonly follows influenza when the blood-pressure has been reduced from 30 to 50 points, to regain this loss following a course of Adreno-Spermin Co.* for a few weeks. With the change in the circulatory manifestations, comes a control of the general asthenic subjective manifestations. This is one of the most decisive and encouraging evidences of the value of this form of organotherapy.

SERGENT'S "WHITE ADRENAL LINE"—A dermographical reaction was described as *la ligne blanche surrénale* by Emile Sergent, of Paris (*Endocrinology*, 1917, i, p. 18), upon which a convenient test has been based. The test consists in lightly stroking the skin over the abdomen with a blunt instrument, such as a fountain pen. A positive reaction consists in the appearance, within a few seconds or not more than half a minute, of a pale line or band following the course of the stroking. Gradually this becomes more and more distinct and extensive, so that eventually the line exceeds in size the actual area stroked. The white line attains its maximum clearness in about a minute and persists for two or three minutes before gradually disappearing. This, at least, is what is to be expected in well-defined cases of adrenal insufficiency—the only instance in which the test has any real value. This sign does not always occur in every case, and is therefore of only supplementary diagnostic value.

ASTHENOCORIA—A simple test is suggested by C. F. Arroyo, of Tampa, Florida (*Med. Jour. and Rec.*, Jan. 2, 1924, cxix, p. 25), who claims it to be of value in determining the presence of adrenal insufficiency:

"When exploring the pupillary reflex I found that in the iris of these cases, although reacting readily to light, the contraction was flabby, lazy, in a word, asthenic. By making the patient look at the light we see that immediately after the initial miosis the pupil starts to dilate slowly as if it does not want to, seems to try to contract again, but the dilatation gains the upper hand and, after a fight between miosis and mydriasis lasting for about forty seconds, the pupil remains dilated in spite of the persistence of the exciting agent. This sign is constant and present in all cases of hypoadrenia and in all its clinical forms. In the normal individual it does not appear, as I have investigated. All patients presenting this sign, which I should like to call *asthenocoria,* have been benefited by suprarenal medication."

4. THE PANCREAS

The laboratory is of outstanding value in the diagnosis and study of diabetes mellitus. The examination of the urine for specific gravity, sugar, acetone, and diacetic acid is so well known as to need only the merest outline.

HYPERGLYCEMIA—The estimation of the blood sugar is the most valuable index of pancreatic endocrine dysfunction. This test may be carried out in several ways, which are fully outlined in any laboratory manual. The variations in the blood sugar are an invariable guide to carbohydrate tolerance which, while not entirely under the control of the pancreatic internal secretion or the Langerhansian hormone, is regulated largely by it.

THE ACID BALANCE—Acidosis, a condition commonly associated with advanced stages of diabetes but not infrequently found under other circumstances, is studied by the estimation of urinary acid (acidimetry) and by certain technical procedures that will only be mentioned here: (1) Van Slyke's test of the alkali reserve, (2) determination of the alveolar carbon dioxide tension.

5. THE PARATHYROIDS

BLOOD CALCIUM—Since the blood calcium reveals the principal evidence of hypoparathyroidism, its study (method of Kramer and Tisdall, or modifications thereof, preferred) has become much more appreciated. Normal calcium figures are from 9 to 10 mg. per 100 cc. of blood. A decrease in this index calls for parathyroid therapy, because the parathyroid hormone (16) raises such an abnormal figure, thereby confirming our suspicion.

Since blood coagulation is dependent, among other things, upon the availability of calcium in the blood, a test of the clotting time is of interest in the study of hypoparathyroidism and other endocrine disorders, especially of the liver. The test is easy: A small puncture is made in the lobe of the ear and the time taken for the blood to coagulate is noted. Normally this varies from two to three minutes, but in different disorders the time may be lengthened to ten or fifteen minutes.

6. THE THYMUS

FLUOROSCOPY—The X-ray examination of a persistent thymus is the best diagnostic confirmation. Fluoroscopy is best since the patient can be moved.

Some years ago, I suggested that the thymic shadow could be identified more easily by comparing the shadows in the claviculo-sternal angles. X-ray therapy of a persistent thymus often gives striking therapeutic-diagnostic confirmation. When a true thymus shadow is noted, it frequently is found to be displaced by certain movements made to order by the patient while under the screen. For instance, breathing may displace the shadow upwards, and tipping the head back does the same thing. Many "thymus shadows" are products of the imagination. Confirm the presumed diagnosis by careful percussion.

7. THE LIVER

The hepatic detoxicative capacity is measured by certain liver function tests. As yet, no test is of value alone, but several together give dependable information. The tests used most are: van den Bergh's test for the icterus index, both direct and indirect reaction; Widal's so-called "hemoclastic crisis"; Rosenthal's bromsulphthalein dye elimination test, and the determination of the urobilinogen. None of these alone is sufficient. Certain urinary findings and tests are of supplementary value.

A positive van den Bergh reaction for the presence of urobilin in the serum indicates excessive destruction of the blood in the spleen or elsewhere. The direct van den Bergh is a measure of the permeability of the liver cells as well as of the patency of the bile ducts.

WIDAL'S HEMOCLASIA TEST—An interesting and novel procedure that has been employed to a considerable extent recently is that known as the digestive hemoclasia test, introduced by F. Widal, of Paris (*Presse méd.*, Dec. 11, 1920, xxviii, p. 893; also *Jour. Am. Med. Assn.*, March 28, 1925, lxxxiv, p. 1002), for the determination of the proteopexic function of the liver. The procedure is quite simple: The leukocyte count is made on a fasting

stomach, and a glass of milk (200 Gm.) is drunk, after which further counts are made at intervals of twenty minutes during the next hour. If the liver is normal, the leukocyte counts are approximately the same throughout; but, when hepatic dysfunction is present, there is a marked destruction of white cells during the first hours of digestion. The explanation of this phenomenon is that the improperly disintegrated food proteins pass from the intestine into the portal vein. Certain of these proteins are held back by the liver—the so-called "proteopexic function." When the liver is unable to retain these improperly digested proteins, they pass into the circulation, where they exert a destructive action on the blood-cells—digestive hemoclastic crisis, or hemoclasis, as it is called. This crisis is accompanied by a syndrome that is characterized by leukopenia, inversion of the leukocytic formula, diminution of arterial tension and refractometric index, and increased coagulability of the blood. Of his test, Widal says:

"Like all other biologic tests, it is not infallible; but it rests on an indisputable physiologic foundation, and it is perfectly harmless. . . . This test acquires an important practical value in what we have termed latent hepatism when, in the absence of any obvious sign of liver trouble, the clinician wishes to be informed of the integrity or otherwise of the organ. In such cases the slightest functional disturbance acquires undeniable diagnostic value."

Some good work with the digestive hemolysis test of liver function has been done by A. L. Levin, of New Orleans (*South. Med. Jour.*, Nov., 1924, xvii, p. 831). This is especially interesting in view of his tests of the influence of an extract of liver upon this phase of hepatic activity.

THE MEASUREMENT OF DYE ELIMINATION—Of the various tests of the capacity of the liver to eliminate dyes, Rosenthal's is the best. This test, sometimes called the Rowntree-Rosenthal test, makes use of phenoltetrachlorphthalein (occasionally called "tetrachlor"), and is made as follows: Five mg. of the substance per kilogram of body weight is injected intravenously, and specimens of blood are withdrawn after fifteen and sixty minutes. A colorimetric test is made, the normal percentage of dye in the blood after fifteen minutes ranging from 3 to 5 per cent. It should be gone entirely after an hour. If the liver function is defective, the dye is retained, and a quantitative colorimetric method gives one a good idea of the extent of hepatic impairment. In those whose liver function is deranged, the serum, after the same lapse of time and after the addition of sodium hydroxide, will still show certain quantities of the coloring matter. The dye content of the serum during the first hour after injection is higher in hepatic subjects than in normal ones, and in the case of the former it may be perceptible some hours after injection. The

color is compared with that of a series of graduated solutions. The solution termed 100 per cent. represents the degree of coloration that would take place in the serum if the injected dye were mixed with the total quantity of blood (about one-twentieth of the total body weight). If, for example, by comparison with standard solutions the serum is found to have a dye content of 5 per cent., it is known that 95 per cent. of the total injected dye has been removed from the serum by the liver.

THE URINARY ACIDITY—To me, the difference between liver disease and liver dysfunction is important, and liver function testing to date appears to be chiefly a means of determining whether some serious disorder is present or not. Considering that the functional disorders are infinitely more common, it seems that some other tests should be more helpful. For instance, R. Glénard, of Paris (*L'hôpital,* 1926, (A) xiv, p. 133), pointed out that the liver regulates the acid-base equilibrium; that the liver is a reservoir of alkaline ions intended to balance variations in the hydrogen-ion content of the blood. Elsewhere, reference has been made to sudden and marked drops in urinary acidity following injections of Anabolin,* as though an alkali had been given. It is suggested that this may be due to catalytic stimulation of the liver to release these alkaline ions. At least, the urinary acid index is frequently very high in hepatic toxemia.

INDICANURIA—Since a high urinary acidity and indicanuria commonly are concurrent, the examination of the urine for indican and indolacetic acid should follow acidimetry. To some, an Obermeyer test is too simple to be mentioned, yet indican and the protein waste products associated with it should be destroyed completely by the liver. The late W. M. Barton, of Washington, D.C., believed that spontaneous indicanuria is dependable evidence of the type of hepatic insufficiency called "hypohepatism" (66). When the accompanying putrefaction is not marked, and consequently there may be only a trace of indican, Barton suggested "the provocative indican test." One mg. of indol is given in the morning on an empty stomach. Specimens of urine are collected every four hours and examined for indican. The liver should be able to destroy this amount, so, if indican appears, one may assume that hepatic detoxication is not normal.

THE URINARY AMMONIA—Another useful urinary test is that for ammonia. The liver should transform into urea all the ammonia products brought to it. In hypohepatism, the ammonia may not be completely changed so the amount excreted naturally increases. In 1911, I called attention to the fact

that the total urinary ammonia (Malfatti's method) may be increased three or four times the normal in cases with high urinary acidity and indicanuria. Another "provocative test" is suggested by Barton: Having determined the average twenty-four-hour ammonia excretion for several days, the patient is given 6 Gm. ammonium acetate by mouth. The twenty-four-hour specimen is studied for ammonia; considerable increase of the ammonia indicates an impairment of functional integrity.

THE SODIUM SALICYLATE TEST—Another urinary test that may be mentioned was devised by M. Roch, of Geneva (*Rev. méd. de la Suisse rom.*, May, 1922, xlii, p. 291), who suggested a test based on the fact that salicylate causes the production of glycuronic acid in the liver. Roch outlines the following procedure: One hour after breakfast, say at 8 o'clock, administer 4 cg. of salicylate of soda. The urine is passed at intervals between 9 and 11, and again between 11 and 1. These specimens are tested separately. A small quantity of each specimen is carefully overlaid on a 1 per cent. solution of perchloride of iron in a test-tube. A violet color at the contact of the two liquids is a positive reaction. The normal liver is capable of completely transforming this amount (4 cg.) of salicylate; at least, it will not allow the passage of sufficient salicylate to cause a positive reaction. This test is not used extensively in Great Britain or America, but it seems that it should be of some supplementary value.

A THERAPEUTIC TEST—Still another test is mentioned, but with some trepidation since it consists in the use of Anabolin* as a therapeutic diagnostic agent. Anabolin is capable of reducing certain functional hypertensions, particularly those in which toxemia results from defective hepatic detoxication (13). It is of no value, however, in the treatment of hypertension of renal or mechanical origin. The supposition is that where Anabolin is of decisive value, the underlying cause of the toxemia and hypertension is in the liver. This may be supported by several of these urinary tests, or by the more generally accepted hepatic function tests previously mentioned.

IV

ENDOCRINE THERAPEUTICS

32. INTRODUCTION

EVERY CLOSE student of organotherapy during his explorations of the endocrine complexities encounters two kinds of difficulties which impede his advance: the confusing findings in the clinic and the conflicting statements in the literature.

There have been many misunderstandings about organotherapy; and, as one frequently finds the clinicians saying one thing and the physiologists another, it sometimes is hard to know what to believe.

The writer long since has recovered from the bewilderment that was created by the contradictory views and assertions that marked the early era of endocrinology and which, after all, were quite natural, owing to the difficulties of a problem that presented so many novel phases. I really think, however, that we have found a satisfactory way to evaluate endocrine therapeutics. It is that unscientific procedure sometimes known as the "try-and-see method." The test is the test of results. But, says one, "It may be coincidence." Another adds, "It might have happened anyway." An experience may, indeed, be an incident at first; the second time it occurs, it might be a coincidence; but soon thereafter, with repetition, it becomes a conviction. It is safe to say that one positive observation has greater evidential value than several negative ones.

Many an advance in endocrinology has originated in the clinic. Empiricism has justified itself time and again. Surely we have not yet come to the end of endocrine knowledge, when we can still hear the echo of those who cry "still in its infancy." Let us take this well-meant criticism, and by careful clinical study and application help this lusty infant to grow into a useful manhood.

The information submitted in this section is intended to serve as a mental hormone to the reader's interest and action. It is hoped that it may arouse or set in motion a train of thought and procedure that will accomplish something worth while in his clinical experience. My personal advice to the reader is not to take for granted the information collated here. Rather, let it serve as a mental sign-post to a goal that he must reach by his own effort. I repeat

the seed thought from the famous Edinburgh divine, Dr. Hugh Black: "Reading is dangerous because it is so often a substitute for thinking."

Although the facts as outlined may sound reasonable, and the prospect of applying them in a given case may seem very alluring, experience emphasizes several outstanding points of warning:

First, the diagnosis must be right or nearly so.

Second, the endocrine part of the clinical problem has to be given its proportionate value, and the patient, rather than his symptoms, should be treated.

Third, the treatment must be thorough and the endocrine phase of it should be given as only a part of the procedure rather than as the sole measure.

Fourth, the remedy must be potent and administered in doses large enough and continued long enough to accomplish what is expected of it.

Last, but most important and vital of all, the results, in the majority of cases, will depend upon the response of the patient's own endocrines to the stimuli offered by the organotherapy.

Here, in this last consideration, lies the nucleus of the success or failure of our efforts. Attention has been paid to this elsewhere (page 63), but it cannot be emphasized too much.

So we proceed to a consideration of the possibilities of endocrine therapy as *a part* of the treatment of each condition enumerated. Whether it be a true endocrine disease or a problem with an incidental endocrine factor that needs attention, I make these suggestions with a confidence based not only on personal clinical experience, but also, in most instances, on the extended experience of many others, at home and abroad, as outlined in the literature on endocrinology.

Perhaps some explanations regarding the arrangement of this section should be made. The aim is to facilitate the use of this material for reference by practising physicians. Instead of discussing thyroid disorders per se, it seems more practicable to start from the standpoint of the patient and his disorder rather than the individual endocrines and their diseases. Hence the syndrome instead of the gland is at the beginning of each item. In virtually all reference works on the subject, the disorders of internal secretion are considered under endocrine headings. Here the reader will find that, besides the comparatively few true endocrinopathies, many non-endocrine conditions are given more or less extended consideration because of the importance of some commonly associated endocrine upset or the likelihood of clinical benefit from the associated use of an endocrine measure.

The magnitude of the literature precludes the free use of bibliographies, so only where it seems to be especially advisable is a reference given.

33. ACHONDROPLASIA

CHONDRODYSTROPHY, SOMETIMES known as *achondroplasia fœtalis* or achondroplastic dwarfism, has been considered by some to be an endocrine dystrophy, which it may or may not be.

Several authors have called attention to the fact that the disease starts in utero before glandular activity begins, and so cannot be due to any defective internal secretion. This does not, however, preclude the possibility of an underlying endocrinopathic cause in the mother. At least, Pierre Marie, the famous Paris neurologist, held that achondroplasia is a general dystrophy comparable with myxedema. It should be remembered that it is entirely possible for an endocrine dysfunction to be superimposed upon a non-endocrine disease, thereby complicating the diagnosis.

Achondroplasia is a moderately rare form of dwarfism in which the length of the body is excessive in comparison with that of the limbs; or, to put it another way, the length of the legs is very much less than it should be in comparison with the length of the trunk. Besides the short, stunted limbs, the bridge of the nose is quite uniformly depressed, the hands and feet are short and thick, and the buttocks are often prominent, causing the phenomenon known as "saddle back." The relative shortness of the limbs and the length of the trunk are striking even in early infancy.

Achondroplasia apparently is a growth disorder of the cartilages forming the epiphyses. It is most common and most marked in the long bones, hence the peculiarity mentioned above.

It has been suggested that in precocious puberty, where closure of the epiphyses is abnormally early, there is a shortening of the extremities that may simulate the picture of achondroplasia. The consensus, however, is that there is no reason to believe that true fetal achondroplasia is the result of dyscrinism.

The diagnosis is never very difficult. The typical dwarfed appearance is accompanied by an equally typical gait or waddle, and a normal intelligence differentiates achondroplasia from cretinism. Further, the cretin and the Mongol do not develop sexually, while in the achondroplastic the gonads mature and usually function normally. The skin and hair are normal, while the protuberant abdomen so typical of cretins is absent. The peculiarity is transmissible, as I have seen personally in a near-by family.

The treatment of achondroplasia is virtually futile. Organotherapy has been tried repeatedly, especially pituitary feeding with and without thyroid. While benefit can come from its influence upon associated endocrine defects that may be present, the real difficulty invariably remains unchanged.

34. ACIDOSIS

AT LEAST four of the most common forms of hypocrinism directly influence the acid balance, and a tendency to acidosis is closely related to dyscrinism.

The sluggish cellular activity, such as is found in moderate and major degrees of hypothyroidism, causes a toxemia of which acidosis is an invariable part. Acidosis *always* accompanies myxedema. The abnormal cellular breakdown products, if not actually acid, are amines that act as do the amino-acids and deplete the body's reserve of alkalies. As has been seen (24), there is evidence that one of the thyroid principles is really a deaminizing hormone.

Particularly in cases accompanied by hypoadrenia, the slowing of the muscular chemistry causes an accumulation of muscular wastes or fatigue poisons, of which lactic acid is one that has been definitely identified. Hence adrenal insufficiency also leads to acidosis. As a matter of fact, the symptomatic benefit that follows the administration of Adreno-Cortin* to patients with cancer (44), is believed to be brought about by the increased destruction of the muscle wastes that the cortical hormone helps to destroy. This also appears to be the reason for the frequent control of the pain in these cases.

Again, in the condition of lime starvation, or hypocalcemia, the defect in calcium fixation, now known to be connected with hypoparathyroidism (81), removes one of the normal detoxicating agencies that ordinarily neutralizes the acid wastes; hence the tetany and other evidences of hypoparathyroidism.

Further, if the liver is failing to anabolize the toxic waste products that are brought to it in the portal blood, hypohepatism (66) is liable to have associated with it a greater or less degree of demineralization, because these waste products are either actually acid or of an acid nature. There is a subtle connection between this phase of acidosis and allergy (36).

Because acidosis is a particularly dangerous sequel of diabetes mellitus, alkalinization or remineralization is always extremely important.

It may be said that *every form* of cellular inaction, whatever the endocrine cause, produces acidosis. Therefore, when endocrine defects are known to exist, it is wise to look for acidosis or demineralization.

Freeing the organism of acid wastes by chemical neutralization not only reduces the acidosis but also lessens the burden of the endocrines that we are attempting to assist. This measure thereby cooperates directly with the endocrine therapy.

Since acidosis is such a very common feature of dyscrinism, it will be necessary to refer to it in a number of the chapters that follow. Special attention is called to remineralization as a supplementary therapeutic measure in Chapter 100 of the Appendix.

35. ADRENAL DYSFUNCTION

Addison's Disease—Asthenia and Hypoadrenia—Adrenal Susceptibility—Adrenal Therapy—Terminal Hypoadrenia—Hyperadrenia—Adrenal Neurectomy—Hypernephroma.

WHEN THE reader fully appreciates the part that the adrenal glands play in the economy, it will be very obvious that adrenal dysfunction must be almost an every-day matter.

Addison's disease and adrenalin may be considered as innocent impostors, for, by the device of their own magnificence, they have for years kept the medical profession in incuriosity about the other adrenal phenomena. The early knowledge of the adrenal medulla and the extreme potency and utility of adrenalin have obscured the importance of the adrenal cortex and the possibilities of cortical therapy. Addison's disease, while rare, is so very dramatic that some of us have had to fight for even the recognition of minor "insignificant" dysadrenias, which we believe to be more important because they are infinitely more common and much more likely to respond to treatment.

ADDISON'S DISEASE—Ultimate adrenal disease, with structural damage amounting eventually to complete loss of the endocrine tissue, is known by the name of the one who first described it in 1849, Thomas Addison, of Guy's Hospital, London. The picture is typical, the symptoms of adrenal insufficiency differing only in degree. As Addison succinctly put it in his monograph, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," published in London in 1855:

"The disease develops in the third and fourth decades of life, usually quite insidiously, with adynamia and apathy. To these are added disturbances of the digestive tract (constipation, often alternating with diarrheas), and pigmenting of the skin and mucous membranes: the patients succumb under a gradually increasing cachexia, not rarely with stormy terminal manifestations; autopsy most always shows disease of both suprarenals, mostly tuberculous caseation."

Addison's disease is a chronic terminal destruction of the adrenals, usually due to tuberculosis, cancer, or chronic inflammation. Peculiarly, it is more common in men than in women.

The picture of addisonism is one of intense depletion; the asthenia is progressive and eventually complete. In the circulatory system, muscular atonia manifests itself in a very low systolic tension, poor circulation, and subnormal temperature. In the digestive system, it causes stasis, ptosis, slow emptying of the stomach with flatulence, bulimia, etc., and putrefaction of the intestinal contents with much toxicity and usually constipation, which alternates with

diarrhea. Its effect on the voluntary muscles is a fatigue of maximum degree.

Pigmentation or bronzing, involving principally the head and neck, is characteristic, though it may be found anywhere on the skin and mucous membranes, especially where pigmentation normally is found. Patches of pigment are often found in the mouth, and in terminal cases the tongue is pigmented, looking as though coal dust had adhered to its sides especially.

Addison's disease cannot be diagnosed early, since the beginning of adrenal damage causes only hypoadrenia (*q.v.*) with none of the maximal findings pathognomonic of true Addison's disease. Serious hypoadrenal symptoms, particularly in patients with a previous history of tuberculosis, should lead to a suspicion of early addisonism. In several cases I have discovered pain and tenderness in the adrenal area, sometimes on only one side. Hypoglycemia is the rule; indeed, the blood sugar may be so low as to cause convulsions. In these cases efforts should be made to restore the sugar balance.

The treatment is general: rest, sunshine, diet, and alimentary care. Organotherapy renders dramatic symptomatic service, but it does not change the prognosis, despite the really great encouragement given by the perfection of the adrenal cortex hormone.

In his contribution to Cecil's "Text-Book of Medicine" (Philadelphia, W. B. Saunders, 1930, p. 1191), Walter Timme, of New York, has this to say about the treatment of Addison's disease:

"Supportive treatment for the asthenia is desirable. Suprarenal substance (dried gland) may be given in doses of 1 gr. after meals twice daily, or small doses of thyroid (from 1/10 to 1 gr. daily) and sodium iodide (5 gr. daily). These may be supplemented with small doses of pituitary (dried gland, from ¼ to ½ gr. daily). All these substances tend to increase the quantity of sugar in the blood and to combat the asthenia."

The reader's attention is called to the foregoing advice regarding pluriglandular therapy and the reason given for it.

Personally, I use very much larger doses of adrenal substance. Possibly the reason for Timme's low dosage is that he refers to *total* substance rather than to the cortex. Frequently one can give Adreno-Cortin* in doses of 1 capsule every three hours (six a day) with decisive improvement. Each 5½-gr. capsule represents 31 gr. of fresh cortex tissue *as free as possible from epinephrine.* (There is approximately 0.35 per cent. of epinephrine in the finished powder.) This gives a daily dose of adrenal substance more than eighteen times that recommended above. Tolerance to this remedy varies, and in some cases large doses cannot be taken because of abdominal cramps.

But it is the solution of the cortical hormone that offers greatest encouragement in the symptomatic treatment of these cases. Much work has been

done in perfecting this remarkable active principle and in separating it from epinephrine (9). Suffice it to say here that Leonard Rowntree and his associates at the Mayo Clinic have treated fifty-seven cases of Addison's disease with a cortical hormone prepared by Swingle. They say (*Jour. Am. Med. Assn.*, Jan. 24, 1931, xcvi, p. 231):

"We are inclined to believe that the cortical hormone is as effective in meeting the crisis of Addison's disease as is insulin in diabetic coma. Although somewhat less prompt and dramatic in action, the results are almost equally striking. Danger lurks in every exacerbation. In the cortical hormone we apparently have a reliable remedy. With unlimited supply of the hormone, it is possible that patients may be completely rehabilitated. This, however, is a matter yet to be determined."

Adreno-Cortin* has been used in a number of cases of Addison's disease. The ambulatory patients were improved very much more satisfactorily than were those in the last stages, all of whom died eventually. The clinical effects of large doses, however, were amazing. For instance, after an injection of 20 cc. one patient felt so much temporary strength that he got out of bed and walked around the room—quite a spectacular accomplishment in view of his condition and the fact that he died a few days later.

Notwithstanding these gratifying results from adrenal cortex therapy, it is hard to believe that the structural damage so usual in Addison's disease can be overcome, and harder still to believe that the physiological substratum that originally permitted the development of the adrenal difficulty will not cause its eventual return. However, marked symptomatic improvement from this therapy is demonstrable beyond question. To me, the important hope is not that we shall be able to establish a cure for Addison's disease, but rather that, by applying our knowledge of adrenal therapy and by thoroughly acquainting ourselves with the symptoms of every-day adrenal distress, we shall be able to interpose in time to spare the complete destruction of some of the body's most valuable fighting forces which have to take the brunt of the battle in an infinite number of our common strains and stresses—emotional, toxic, infectious.

Some of the problem cases are quite puzzling, and confusion is frequent. The following experience is an illustration: A certain patient was seriously ill; he was markedly depleted, with a very low blood-pressure. The skin became quite bronzed, especially that of the hands and face. After suitable treatment, the blood-pressure returned nearly to the average, remaining at about 115/60. The asthenia also was largely overcome, but the bronzing remained. Now, some years later, this patient comes again with a new and similar picture superimposed upon the remnants of the previous one, and

the doctor is at a loss to make a diagnosis. The previous history and pigmentary peculiarities suggest that this patient had something akin to Addison's disease, perhaps in less ultimate degree than those usually diagnosed as true Addison's disease. Is it not possible for an endocrine gland to be seriously damaged and then, with an abatement of the process, to have the damaged area scarred over with a compensatory hypertrophy or functional service in the remaining sound tissue? As such a phenomenon undoubtedly happens in tuberculosis of the lungs, might it not occur also in tuberculosis of the adrenals?

ASTHENIA AND HYPOADRENIA—The picture of depletion and asthenia, with hyposphyxia (circulatory stasis, cold extremities, low blood-pressure), subnormal temperature, reduced tone, and a typical run-down state, is one of the most common clinical findings. It accompanies toxemias, acute or chronic; it is a peculiarly marked feature of the postinfluenzal let-down; it is an integral part of the nervous breakdown; it is a part of the convalescent syndrome.

We are indebted to Emile Sergent, the Paris internist, for the conception of *l'insuffisance surrénale*. In 1899, with Léon Bernard he showed how toxemias, acute or chronic, deplete the adrenals to a degree that makes hypoadrenia a routine problem in all phases of medical practice.

In my 80-page monograph, "The Adrenals in Every-Day Medicine" (1923), scores of clinical and autopsy findings were collated to emphasize the reality of a syndrome that was then being overlooked. It is *still* being ignored by many physicians, but its reality is no longer seriously contested.

In an article in *Time* for February 9, 1931, on "Dowsers" (those who locate underground water by the unexplained use of the divining-rod), the editor says:

"When a pure-hearted scientist meets a phenomenon that he cannot explain, he humbly admits his ignorance and asserts his hope that future science may be able to explain all things. But many a scientist of high standing and great ability is quick to discredit what he cannot explain."

This statement is quoted here because it so aptly illustrates a state of affairs that concerns hypoadrenia, the every-day occurrence of which had come into prominence and quite wide acceptance as the postinfluenzal asthenia was discovered to involve the adrenals, especially during the influenza epidemics of 1918 and 1919 (69). A prominent South American clinician, A. Ricaldoni, of Montevideo, Uruguay, wrote at the time (*An. de Facul. de med.*, July-Aug., 1919, iv, p. 553):

"This adrenal insufficiency is inseparable from influenza itself . . . the adrenal insufficiency of influenza accordingly is more fundamentally significant than that which may appear in all or nearly all of the general infections and many forms of intoxications."

It happens that one of those to whom we are indebted for the perfection of the cortical hormone, the late George N. Stewart, of Western Reserve University, Cleveland, was frank in his criticism of the numerous clinicians who attributed this asthenic syndrome to functional adrenal depletion. It was a case of a scientist's being "quick to discredit what he cannot explain," for Stewart's studies of the adrenal glands convinced him that "the adrenal hormone"—then, of course, the *medullary* hormone—was not essential to life, and could not replace the adrenals when experimentally removed. So he called this conception of hypoadrenia "the fourth dimension" in medicine, and apparently many of his colleagues believed him. Commenting on the reports of Ricaldoni (above), Pende, Josué, and others, Stewart says (*Endocrinology,* May, 1921, v, p. 283):

"In reading this paper and many others by 'clinical endocrinologists,' especially the French and the Italians, the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded, and 'nothing is, but what is not.'"

Referring particularly to my own oft-repeated insistence on the importance of adrenal insufficiency and the still greater importance of adrenal support, this same writer remarked:

"On the whole, then, it must be granted that hitherto the attempts made to evoke in animals a well-marked syndrome characteristic of adrenal deficiency, have been singularly disappointing. The contrast is great when we leave this desert, where the physiologists and experimental pathologists have wandered, striking many rocks but finding few springs, and pass into the exuberant land of clinical endocrinology, flowing with blandest milk and honey almost suspiciously sweet."

An excellent answer to this criticism was made by Emile Sergent, to whom we in America give a large share of the credit for our present convictions regarding hypoadrenia other than Addison's disease. Some months after Stewart's paper was published (from which the foregoing quotations are made), Sergent published a very mild retort to this harsh criticism. It was entitled "L'insuffisance surrénale devant les récentes critiques des physiologistes" (*Presse méd.,* Oct. 12, 1921, xxix, p. 813), from which the following is translated:

"Acquisitions derived from clinical observation cannot be regarded as non-

existent. I may be permitted, in this connection, to raise my voice against the somewhat excessive criticisms made by Stewart in his recent article (*loc. cit.*). I think that the best and most courteous rejoinder that I can make to this eminent physiologist is that he does not know French sufficiently well to have thoroughly grasped the thought of the French clinicians. By way of proving this statement I have ascertained that he attributes to us, quite gratuitously, the view that adrenal insufficiency is insufficiency of the secretion of adrenalin. This was never our thought, and by way of assurance on this point I will state once again that, with L. Bernard, I described the syndrome of acute adrenal insufficiency in 1899 and that adrenalin was discovered in 1901, *two years later.*

"Moreover, I recently had the privilege of chatting with Prof. E. Gley upon this question that interests us both so vitally, for varying reasons, and I had the satisfaction of ascertaining that he shared my view. I was too well acquainted with his scientific mind to doubt for one moment that he attached no value to facts rigorously observed by clinicians."

It happens, however, that this great physiologist, Gley, for years had opposed Sergent's clinical conclusions, as is evident to any who will read his article in the *New York Medical Journal* (July 6, 1921, cxiv, p. 9). Now, all is changed, and in several reports from the same Cleveland laboratory (*Jour. Am. Med. Assn.,* May 11, 1929, xcii, p. 1569) we find another story voiced in an entirely different tone telling of the isolation of the adrenal cortex hormone by G. N. Stewart and J. M. Rogoff, of convincing laboratory experiments, and of early clinical successes—a reversal of opinion that is complete.

So the common endocrine syndrome variously known as hypoadrenia, adrenal insufficiency, or minor addisonism is so vital that the reader will find it mentioned many times in this book. In fact, the purpose of this book is best served by considering the subject of hypoadrenia as a symptom of a number of common disorders. For further information on this subject, therefore, the reader is directed to the consideration of Allergy (36), Cachexia (43), Hypotension (45), Common Colds (47), Convalescence (48), Intestinal Stasis (53), Asthenopia (56), Influenza (69), Dementia Præcox (71), Muscular Disorders (74), Narcotic Addiction (75), Neurasthenia (77), Senility (88), Surgery (90), and Tuberculosis (94).

ADRENAL SUSCEPTIBILITY—Without a doubt some people are more susceptible to functional adrenal depletion than others. Whether due to an emotional instability, a susceptibility to subtle toxemias such as allergy, or a low resistance that makes the patient a frequent sufferer from colds or other infections, the adrenal glands are more easily depleted and the customary fatigue syndrome is ever present. One attack predisposes to another, and, when

they follow in fairly close succession, it is easy to see that the previous functional depletion can actually develop into structural damage.

During the Great War two French physicians, finding themselves with a crowd of refugees in the wine cellars of Lille, made use of their enforced idleness by carefully studying the reactions of several hundred persons. Bombardment showed two effects: (1) a sudden circulatory change, including increase in the blood-pressure, (2) a reduction in the arterial tension soon after the hypertension. Several frequent attacks caused more disorder than the same number more widely spaced, the reason evidently being that the patients had not had time to recover their balance. Certain of these persons did not respond well during the intervals, so these doctors concluded that age, nutrition, and toxemias predispose to damage of the adrenals. In these less resilient individuals, the blood-pressure became lower and the adrenals responded less satisfactorily after each successive bombardment, until in some cases death actually followed the emotional overstrain.

Tuberculosis is one of the most frequent causes of hypoadrenia (94) just as it is the usual cause of Addison's disease. In the latter, of course, there is a localized bacterial invasion with later inflammation and caseation; but in the former the tubercle toxemia itself depletes the adrenals. The malnutrition hastens it, and the dire need for the services of these organs puts a strain on them, making them doubly susceptible to permanent damage.

Another cause of hypoadrenia is given consideration elsewhere (75), but it is so common and so frequently overlooked that it may be mentioned once more. Alcohol, coffee, tobacco, and kindred stimulants predispose to adrenal depletion and undoubtedly make these organs more susceptible to whatever factor may be depleting them, and also prevent the beneficial action of adrenal therapy. The conclusion is justified that, if taken in excess, they will depress the adrenal functioning; this is borne out by Sajous and many others. The same result follows the habitual use of narcotics and even the non-narcotic sedatives. A vicious circle is formed, for after the supposed "benefit" from the stimulant has worn off, the whole endocrine mechanism is depleted, and consequently there is need for further stimulation, which the already overstimulated system can ill put up with. Here lies one of the chief reasons for failure from adrenal support.

ADRENAL THERAPY—The therapeutic possibilities of the two adrenal hormones—the chromaffin hormone, or adrenalin; and the cortical hormone, or Adreno-Cortin*—make this a subject of cardinal importance, for the miracles of adrenal therapy are no less real or frequent than those of thyroid therapy or any other form of organotherapy.

As with other endocrine measures, adrenal therapy is used to replace that which is missing—as in true Addison's disease—and to homostimulate or reestablish waning function. This is not done with adrenalin, for the syndrome of hypofunction of the adrenal medulla is of negligible clinical interest in comparison with cortical insufficiency, *i.e.*, true hypoadrenia.

On the other hand, adrenalin is used as a drug, its vasomotor action being of service in both medical and surgical treatment. It is useful in asthma and hay-fever, relieving conjunctival itching, opening the nasal passages, and diminishing secretion. The solution is utilized in the auditory canal, in the bronchi, in the esophagus, and in the urethra, and may be swallowed for its local effect in the stomach. Added to cocaine or other local anesthetics, adrenalin enhances the effect by constricting the vessels and retarding absorption, thus also diminishing systemic and toxic action. It is widely used as an astringent and hemostatic. Perhaps the most important therapeutic use of adrenalin is as a circulatory stimulant. Until the perfection of the cortical hormone, adrenalin was used in the course of influenza, pneumonia, typhoid fever, cholera, streptococcic and staphylococcic infections, and other depressing maladies to sustain general vigor and support the circulation. Other indications for its use are heart stoppage—as in an anesthetic accident—urticaria, serum sickness, anaphylactic shock, angina pectoris, nitritoid crises following salvarsan therapy, and hypoglycemia resulting from an overdose of insulin.

The Muirhead treatment of Addison's disease was developed as the result of the experience of the late A. L. Muirhead, of Omaha (*Jour. Am. Med. Assn.*, March 5, 1921, lxxvi, p. 652), himself a sufferer from this dire malady. It consisted of injections of from ½ to 1 cc. of a 1:10,000 solution of epinephrine twice daily; rectal injections of dried whole adrenal glands, 10 gr. dissolved in physiologic sodium chloride solution; and whole gland or adrenal cortex by mouth to the point of tolerance. Of course, other measures such as rest, exercise, diet, outdoor life, and sunshine, are advised. The perfection of a potent cortex product, however, has obsoleted Muirhead's method.

The older adrenal extract, a total gland product, has been in use for years; and, as we have seen (9), it is virtually a cortex product. Given by mouth in doses ranging from 1 to 5 gr. three or four times a day, it is a tonic and restorative in many depleted states. The procedure that I call "adrenal support" is as great an achievement as any other advance in endocrine therapy —including thyroid, insulin, and liver therapy.

The depleted states already enumerated here and discussed throughout this book are never due to adrenal disorder alone. Obviously Addison's disease itself is never just an hypoadrenia with all the other endocrines working

normally. So we attempt to reestablish endocrine function as a whole. Since the factors that deplete the adrenal system are always general in character (toxic, infectious, emotional), obviously the effects are not limited to one organ or function. The usual causes of adrenal exhaustion also deplete the thyroid, and, in fully 80 per cent. of the cases of hypoadrenia, the thyro-adrenal system is literally played out. Hence my use of Adreno-Spermin Co.,* which combines adrenal substance, thyroid, and spermin (the dynamogenic gonad principle), to control the every-day, run-down, played-out states—tonic organotherapy at its best. These substances are fitted together in a dosage that has been worked out in many thousands of cases. The experience of years has demonstrated this formula to be a tonic of merit, especially in functional depletion of the thyro-adrenal system, due to toxemia, infections, or emotional stress with the outstanding symptoms of asthenia, low blood-pressure, reduced oxidation, subnormal temperature, etc.

Naturally, much of our success with adrenal therapy, as with all other forms of organotherapy, depends upon the responsiveness of the patient's own glands. Thus it is evident that if the adrenal tissue is actually destroyed, as is the case in Addison's disease, it cannot respond to the homostimulative influence of adrenal support, and the treatment fails. Other elements of failure are: not continuing the reeducative treatment long enough, insufficient dosage, ignoring other necessary therapeutic measures, overlooking deficiencies in associated glands, and last—but by no means the least important—a wrong diagnosis.

TERMINAL HYPOADRENIA—In 1903, C. E. de M. Sajous, of Philadelphia, described a fatal form of extreme adrenal exhaustion, which he named "terminal hypoadrenia." It contributes to the death that follows cholera, plague, malignant malaria, and severe burns. Since terminal hypoadrenia was first considered, many hints have appeared in the literature indicating that the adrenals are actually damaged by the severe toxemia. This is referred to again in the consideration of Burns (42) and Influenza (69).

M. Naamé, of Tunis, developed this idea of adrenal exhaustion in his studies during an epidemic of cholera. As a result of his experience, he writes (*Rev. gén. de clin. et de thérap.*, 1912, xxvi, p. 87):

"I am firmly convinced that the cholera syndrome is an acute hypoadrenia due to poisoning of the adrenals by toxins of the cholera spirillum. . . . The attack consists of two phases—the first, bacillary or intestinal, comparatively harmless; the second, toxic or adrenal, frequently fatal."

In a paper on the relation of hypoadrenia to acute infectious diseases and toxemias, read before the French Academy of Medicine (*Bull. gén. de thérap.*,

1912, clxiii, p. 881), Emile Sergent connects certain conditions that may supervene in typhoid fever with the syndrome of hypoadrenia. This is in harmony with his previous efforts to prove that adrenal insufficiency may be observed in all infectious diseases as well as in all severe intoxications. Sergent's theory has come to have great practical importance, as it involves the use of adrenal support in such cases. An acute adrenal insufficiency may be suspected in an infectious disease when agitation, excitement, and fever give place abruptly to prostration, low temperature, and arterial hypotension, with the white adrenal line and a tendency to collapse. Sergent asserts that the not infrequent complete prostration and small pulse found in typhoid fever are signs of adrenal insufficiency. These symptoms attain their maximum in certain severe typhoid cases, even simulating peritonitis or internal hemorrhage, and disappear rapidly under adrenal therapy. Certain complications of convalescence, such as prostration, anemia, psychasthenia, etc., are also due to deficient adrenal activity from subacute inflammation of the adrenals. From the data that he has so carefully gathered, Sergent concludes that the systematic employment of adrenal preparations is justified in all cases of typhoid, and that the extracts of the entire gland are indicated for the severe complications due to acute hypoadrenia. Except in those hypertoxic or hemorrhagic cases that defy all treatment, this method, associated with the ordinary treatment of typhoid, gives considerably better results.

Usually there is little that can be done in the extreme terminal condition because the adrenals are hemorrhagic and destroyed; but the cortical hormone offers some hope because of its substitutive value, and generous doses should be given on the chance that it will replace a part of the essential service expected from the adrenals. The dose of Adreno-Cortin* in such critical circumstances is from 1 to 5 cc. intramuscularly *every hour*.

HYPERADRENIA—Overfunction of the adrenals is a real condition that occurs quite frequently, but, strangely enough, it is of little or no clinical importance. Adrenal irritability is a part of the picture of hyperthyroidism (63) and sympathicotonia (91). Most of us have had personal experiences with it when we have been emotionally upset, as in public gatherings where we had to take part. The symptoms of hyperadrenia are a dry mouth, circulatory imbalance (flushings or chills), temporary hypertension, internal nervousness and tremor, and abnormal perspiration. This is most commonly brought about by the influence of the emotions upon the adrenals, as explained so well by Walter B. Cannon and his associates at Harvard University ("Bodily Changes in Pain, Hunger, Fear, and Rage," New York, D. Appleton & Co., 1915).

Such functional hyperadrenia cannot be controlled, although the causes may sometimes be regulated and the stimuli that are driving the adrenals may be lessened. The picture of hyperadrenia is always a fleeting one, for the adrenal hormones are easily destroyed and, if the stimuli are prolonged, the picture changes to one of hypoadrenia with weakness and depletion as the main symptoms.

During the earlier stages of diabetes mellitus (52), especially in the nervous, emotional type of patient, hyperadrenia may develop into an important factor. In fact, it even may be a part of the etiology of this disease, since the antagonism between the adrenals and the pancreas is well known.

Another manifestation of hyperadrenia may be found as a part of the climacteric upset in women whose change is associated with a considerable increase in the blood-pressure. Without a doubt, the adrenals are involved at the menopause, although thyroid and pituitary dysfunction are most common. In this supposed hyperadrenal hypertension, the suggestion has been made to make use of the known antagonism of the pancreas to the adrenals; hence total pancreas substance (*not* pancreatin) has been employed in these cases (80). The frequency with which both the sympathetic irritability and the hypertension respond to such treatment adds to the impression that hyperadrenia is one of the factors responsible for the circulatory imbalance at the climacteric.

An Italian physician, G. Galatà (*Riforma med.*, Oct. 26, 1929, xcv, p. 1449), in discussing arterial hypertension of the climacteric, states that its usual duration is only a few years. Not infrequently, however, it is prolonged with a progressive course for several years after the cessation of the menstrual periods, until it is sometimes confused with true states of atherosclerotic hypertension. Its chief manifestation is in those women in whom the climacteric takes what might be called a sympatheticotonic course. Galatà performed a unilateral adrenalectomy in a case of grave and obstinate climacteric hypertension, with a resulting fall in the blood-pressure of 55 mm. of mercury on the day of the operation and of 40 mm. more during the three days following. Not only had all means of treatment during a period of eighteen months failed to modify the arterial pressure, but in this patient there had been an obstinate and relatively rapid tendency toward increased tension.

In the consideration of sympathicotonia (91), attention is called to hyperadrenia as a part of the picture, and so a formula such as Pancreas Co.* is recommended as of symptomatic benefit, evidently because of its antiadrenal balancing influence.

ADRENAL NEURECTOMY—George W. Crile, of Cleveland, Ohio, whose studies of the kinetic drive have led to the philosophy known as "anoci-association"—the blunting of harmful association impulses, a method of anesthesia designed to minimize the effect of surgical shock—has made some startling announcements regarding the surgical possibilities in conditions involving the adrenals. Crile considers the relation of the adrenals to the autonomic system comparable with that of the brain to the cerebrospinal system. His reasoning is as follows: The thyroid controls the accumulation of energy in the body; the adrenals, brain, and sympathetic system control the expenditure of this energy.

"Because the entire organism is capable of just so much oxidation—hence so much energy—natural selection endowed the brain and the nervous system with the power of driving one group of organs and inhibiting all the others. The professional man, the business man, the banker, the statesman, the soldier, although achieving their survival by the control of nature's energy in the infinitely complicated web of life, built fear and worry and hate in every tissue and organ of their bodies. Thus the frontal lobe of the brain has conferred survival upon ourselves."

Crile believes that the brain, especially its frontal lobe, shunts energy from other vital parts of the body by draining the capacity of the adrenal glands and the sympathetic. In certain cases in which it is desirable to diminish the kinetic drive, Crile performs a partial or complete denervation of one or both of the adrenals. He claims that such intervention is capable of modifying the grand mal of epilepsy, changing it to petit mal; that there are some good prospects in Raynaud's syndrome; that peptic ulcer may be controlled for varying periods; and that certain cases of hypertension are benefited.

At the Philadelphia meeting of the American Medical Association (June, 1931), Crile reported eighty-four cases in which this shunting was prevented by the operation of adrenal neurectomy, with the result that gastric and duodenal ulcers healed rapidly, exophthalmic goitre subsided, and high-strung, sympatheticotonic persons were calmed down.

This reminds one of the attempt by P. Cottenot, the Paris radiologist (*Jour. méd. franc.*, March, 1924, xiii, p. 116), to control similar conditions, especially essential hypertension, believed to be due to hyperadrenia, by means of deep X-ray therapy to one or both adrenals. Such intervention seems too radical to me, and it is hard to determine how to regulate the extent of its atrophying influence. With regard to Crile's operation, undoubtedly it is based on sound considerations, and the clinical results are as stated; but, as with many cases of hyperthyroidism (63), so with hyperadrenia—the endocrine glands are the victims of circumstances that the surgery does not reach.

HYPERNEPHROMA—Certain neoplastic changes in the adrenal glands cause a condition known as hypernephroma, which clinically is quite different from any of the more usual types of adrenal disease referred to here. Pathologically, these growths may show the structure of simple hyperplasia, running a course without serious symptoms or giving rise to local manifestations of a tumor, or they may assume malignant character and then show great inclination to the formation of metastases. Finally, these tumors may lead to profound alterations in the organism, which, with a certain probability, may be regarded as the expression of hyperfunction of the cortex, and, of course, endocrine in character. Such new growths are quite rare, and it happens that most of those reported have occurred in children.

With the development of such hyperfunctioning cortical tumors in the child's organism, there occur an enormously accelerated development of the body and a premature development of the genitalia. It is suggested that this condition affects girls more frequently than boys. In all cases, the outstanding clinical feature is a premature, excessive development of the secondary sex characteristics and the external genitalia. Further, in most cases there is adiposity, accelerated growth, probably with retention of the infantile dimensions, and accelerated ossification and dentition. The development of the psyche in these children as a rule does not keep pace with the bodily development, and the development of the sexual instinct also is usually retarded.

The relation of the adrenals and the gonads is seen most definitely in the developments that accompany hypernephroma, for in such cases there is an abnormal stimulus to gonad development and function. Precocious puberty has been noted in connection with hypernephroma, and an unusually early or abnormal puberty should direct attention to the possibility of structural changes in the adrenals.

Progeria (46) has been connected with pathology in the adrenal cortex, but autopsy of one of Hastings Gilford's cases failed to confirm this.

Hypernephroma in the juvenile or mature organism is always characterized by a marked influence on the sexual sphere. In women, simultaneously with the development of a hypernephroma there follow cessation of the menses, hypertrichosis of a definite localization (*linea alba,* beard), and obesity. At the menopause the development of hypernephroma apparently gives rise only to obesity. Hirsutism and virilism (97) are also signs of possible adrenal cortex pathology.

The early diagnosis of hypernephroma is very difficult and, no matter whether discovered early or late, the prospect for an effective therapy is very poor. X-ray may be used for lack of something better.

36. ALLERGY

Allergy—Protein Sensitiveness—Idiosyncrasy.

THAT THE endocrine organs play an important role in the symptomatology of the various reactions of hypersensitiveness (allergy) should seem self-evident when it is remembered that most cases of allergy, regardless of their severity, can be completely relieved by the action of an endocrine substance—epinephrine. Many patients also obtain temporary relief from posterior pituitary extract.

My own interest in the postulated relation between the endocrine functions and their susceptibility to certain proteins has had to do chiefly with the attempt to solve the migraine problem by considering it from the standpoint of hypohepatism (66). Then, too, the philosophy underlying my suggested treatment of the vomiting and nausea of early pregnancy (84) is based on the presumption that this condition may be a manifestation of sensitization to the protein waste products of the placenta.

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There is as yet no definite agreement about the relation of the endocrines to allergy, so we shall have to be satisfied with a collation of some of the opinions expressed in current literature. This will, I am sure, arouse the reader's interest in various aspects of the subject. One point of clinical usefulness will emerge from it all, *i.e.*, when allergy is accompanied by evidence of endocrine dysfunction, the successful control of these endocrine features may frequently modify the protein sensitization itself. Certain it is that dyscrinism commonly accompanies allergy. W. W. Duke, of Kansas City ("Asthma, Hay-Fever, Urticaria, and Allied Manifestations of Allergy," St. Louis, C. V. Mosby Co., 1925, p. 145), says that if there is a normal physiologic antagonist to the adrenal medullary principle (and one might easily believe that there is) an overproduction of it might theoretically give rise to a reaction. Duke's ruminations on this subject are interesting and they antedate many of the suggestions now found in the literature. He also says (*ibid.*, p. 138):

"One frequently wonders whether or not certain individuals become sensitive to substances originating in the body proper. Substances absorbed from the alimentary tract are in reality exogenous in origin since the alimentary tract is nothing more than a tube passing through the body, and substances contained in it are outside the body in the same sense that substances are outside the body proper when in contact with the mucous membrane of the mouth or the skin. One would not believe it likely that individuals could become sensitive to and react to substances of endogenous origin which are present constantly in bulk. Substances of this nature should either cause death or give rise to tolerance so that in the course of time patients

should cease reacting to them. However, conditions frequently arise that make one suspect sensitiveness to a body substance which is produced or distributed only under unusual circumstances. This view, however, is difficult to prove. In one case observed by the writer, severe manifestations of allergy appeared each month just prior to menstruation. The attacks were associated with dysmenorrhea, and ceased immediately when the flow from the uterus was established. In three cases, patients suffered a severe attack of allergy coincidentally with the weaning of the baby. The attacks could be relieved by the free use of a breast-pump."

Duke suggests that thyroid extract occasionally may be very beneficial to the allergic patient whose metabolism is below average and whose temperature is markedly subnormal. On the other hand, A. Popea and I. Constantinescu, of Bucharest (*Compt. rend. Soc. de biol.,* March 21, 1924, xc, p. 720), found that patients suffering from hypothyroidism are not easy to sensitize, whereas, when hyperthyroidism is present, sensitization is easily effected. In Guiseppe Pistocchi's research with guinea-pigs (*Arch. per le sc. med.,* 1921, xliv, p. 91), he was unable to detect any modification of the tendency to anaphylaxis after splenectomy or nephrectomy, but removal of the thyroid had a pronounced effect in reducing the susceptibility to anaphylaxis-producing toxins. This was evident even when the parathyroids were removed with the thyroid.

K. Hajós, of Budapest (*Klin. Wchnschr.,* July 16, 1926, v, p. 1330), thinks that disturbances in endocrine equilibrium change the sensitiveness of the patient. He confirmed his opinion by experiments on animals. As a result of this investigation it was shown that, in addition to adrenalin, the hormones of the posterior lobe of the pituitary and of the parathyroid are actually capable of preventing the anaphylactic phenomena when given at the correct time and in the most suitable dosage. Thyroid extract and insulin appear to increase the sensitivity of the guinea-pig, but the influence of the sex glands and of the anterior pituitary on anaphylaxis could not be established in these animal experiments.

There is a relationship between the features underlying allergy and a defect in the mineral balance. Several French authors speak of a derangement of the calcium metabolism in this class of cases, and it is well known that calcium therapy frequently may be helpful in certain anaphylactic manifestations. Whether this can be definitely connected with a shortcoming in the capacity of the organism to appropriate or "fix" lime, or with defective destruction of acid wastes and their precursors with corresponding alkali depletion, has not yet been established. Suffice it to say that the consideration of lime fixation and acidosis may be helpful in the solution of several problems in which allergy is present.

In the *Journal of the American Medical Association* for October 18, 1924 (lxxxiii, p. 1221), Andrew A. Eggston, of New York, states:

"It would seem that any undue taxation of the autonomic nervous mechanism through fatigue, faulty metabolism, hypoendocrine or hyperendocrine function will result in sympathetic reactions, of which vasomotor rhinitis and allergy are related expressions."

Some suggestive clinical coincidences are related by Warren T. Vaughan, of Richmond, Virginia (*Virginia Med. Month.*, Nov., 1924, li, p. 475), who tells of a woman who developed bronchial asthma shortly after an artificial menopause. She was treated for two years, with the elimination of those proteins to which she was sensitive, without any benefit. Three days after the administration of ovarian and mammary extracts, her asthma ceased. Another woman, middle-aged, was sensitive to several food and epidermal proteins. The attacks usually came with her menstruation. She did not respond to removal of the allergens, to autogenous vaccine, peptone treatment, or the intravenous administration of calcium chloride, but promptly recovered following the administration of suitable amounts of thyroid and parathyroid extracts.

In the *Medical Journal and Record* for April 1, 1924 (cxx, p. 41), appears a letter from their Geneva correspondent, in which he tells of a case reported by R. Lavielle. A woman, 23 years old, was suddenly seized with a series of very impressive disturbances. She complained of violent colic and severe headaches accompanied by uncontrollable vomiting in closely repeated paroxysms. The body was covered with a pruriginous exanthema, especially marked on the trunk and upper limbs, while the eyelids were so edematous that the patient could not raise them. The history showed that the menses had begun on the day that these morbid phenomena developed, and, regardless of this fact, the patient had taken a cold plunge in a pond. Because of the chilling, menstruation ceased shortly after the development of the anaphylactic crisis. (Previously the patient had had attacks of urticaria after ingestion of fish or strawberries.) An emmenagogue was given, and in a few hours the menses returned, while at the same time most of the symptoms of shock retrogressed. Only the edema of the eyelids and face was slow to subside, although it had disappeared by the next day.

This typical anaphylactic crisis is interesting merely because of its coexistence with the suppression of the ovarian functions. The absorption of blood consequent upon the arrest of the menstrual flow does not seem to be the cause of the crisis, since, in this case, the albumin entering the organism was not heterogeneous. If the close relationship between the sympathetic system

and the endocrine glands—especially the ovary—is considered, as well as the short duration of the anaphylactic crisis and its severe outburst, it seems logical to suppose that the anaphylaxis was caused by a reflex having multiple manifestations indicating a sudden disequilibrium of the vagosympathetic system.

J. T. Malone, of Portland, Oregon (*U. S. Vet. Bureau Med. Bull.*, April, 1929, v, p. 285), obtained low blood-sugar values in fifteen cases of allergic bronchial asthma associated with a suspected food allergy. The hypothesis of an altered internal secretion of the pancreas resulting in a disturbance of carbohydrate metabolism was suggested as an etiologic factor in certain allergic manifestations; and experimental research has proved that the administration of endocrine preparations has a definite effect on carbohydrate metabolism. The suggestion is advanced that an undetected liver hormone may be involved in the complex etiology of allergic manifestations.

According to Ralph H. Spangler, of Philadelphia (*Jour. Lab. and Clin. Med.*, Oct., 1927, xiii, p. 41), immunologic, laboratory, hereditary, clinical, and therapeutic evidence point to allergy as an etiologic factor in some cases of essential epilepsy. This unusually interesting paper contains the following conclusions:

"Analysis of one hundred consecutive adults with recurring convulsions reveals that in 88 per cent. there was a history of allergy in the ancestors. The total number of ancestors showing allergic manifestations, not including convulsions, was 158, and there were fifty-four allergic manifestations, besides the convulsions, in the patients themselves.

"Gastro-intestinal allergy, as shown by using substitutes for mother's milk, appears to be an important factor in the development of convulsions in the allergic child. In this series of one hundred epileptic patients, 32 per cent. had convulsions in infancy, of whom twenty-four, or 75 per cent., were bottle-fed, and eight, or 25 per cent., were breast-fed. . . .

"When the allergen or causative agent cannot be determined in epileptic patients who have an hereditary or personal history of allergy, and in whom a leukocytosis occurs following a convulsion, non-specific desensitization by venom protein (crotalin) solution, when regulated by the percentage of eosinophile cells in the differential blood-count, has proved of value in decreasing the state of allergy."

A number of writers have expressed the opinion that migraine is, in some respects, very similar to other allergic reactions. As will be seen elsewhere (72), migraine manifests also some clinical points connecting it with defective hepatic detoxication. Hence there is good reason to consider the hepato-endocrine functions in these cases of extreme protein sensitization, and to do everything possible along such lines.

37. ALOPECIA

ONE OF the uniform findings in thyroid disease has to do with the nutrition of the skin and its appendages. In myxedema, for example, dry, brittle hair is almost pathognomonic. When loss of hair is definitely connected with hypothyroidism, it may be modified by giving the needed thyroid therapy. But this does not warrant the assumption that the hair follicle can be made to produce another hair by recourse to organotherapy. Besides, there are undoubtedly many more local causes of baldness than there are endocrine ones, and they, of course, should not be expected to respond to glandular therapy.

Several cases of alopecia totalis have been seen that were clearly a part of an endocrine complex. In two of these the response to the much needed regulation of the endocrine upset was accompanied by a good growth of hair on the scalp. On the other hand, one case, seen in Toronto some years ago, failed to respond to the same kind of treatment, although it was followed out most thoroughly.

There are numerous reports in the literature. For example, M. B. Gordon, of Brooklyn (*Arch. Dermat. and Syph.*, June, 1928, xvii, p. 817), describes a case of almost universal alopecia areata that had persisted for nine months and had resisted all local treatment. The administration of thyroid extract was followed by immediate improvement, which continued until virtually all the hair had returned.

Prior to this, Samuel Ayres, of Los Angeles, recognizing the endocrine origin of certain cases of alopecia and vitiligo, reported a clear-cut example of such association in the *Archives of Dermatology and Syphilology* (Oct., 1923, viii, p. 502). Unfortunately, the case was reported merely because it was a good example of thyroid involvement in alopecia, and the outcome of treatment was not given.

Some interesting endocrine findings connected with alopecia were outlined by J. Strandberg, of Stockholm (*Acta med. Scandin.*, 1922, lii, p. 165). He reported nine cases, three of them in women and six in men, in all of whom alopecia areata had progressed to almost complete baldness. In none of these were endocrine disturbances demonstrated with certainty. Syphilis was shown to be present in only one case. Two had dementia præcox. In three of the cases there was a renewed growth of hair as a result of thyroid treatment, which was given in tablets of 2 or 3 gr., t.i.d. In two other cases the treatment was of too short duration to warrant any conclusion. In one case that did not respond to thyroid medication, a new growth of hair appeared during a subsequent pregnancy, only to disappear again at the onset

of menstruation. In one of the dementia præcox cases the patient was not benefited by organotherapy, but later a hirsute development set in with improvement of the psychic condition.

An interesting note appears in a collective abstract published in *Dermatologische Wochenschrift* (Feb. 7, 1931, xcii, p. 210), stating that A. Buschke, the Berlin dermatologist whose work with thallium acetate made its therapeutic use an accepted practice, has employed this drug in the treatment of alopecia areata, which had defied all other measures, to produce complete temporary depilation. On regrowth of the hair it was found that previously denuded areas of alopecia had recovered. A similar success is claimed in a case of monilethrix, an infection peculiarly resistant to all treatment. It happens that Buschke and others hold the opinion that thallium acetate acts by way of the endocrine glands, although the biochemical mechanism is far from clear.

The following from the *Journal of the American Medical Association* (March 31, 1923, lxxx, p. 945) is a fair statement, the truth of which still applies:

"There is some ground for believing that certain forms of baldness, particularly extensive diffuse baldness, may be due to endocrine disturbance. The most tangible reason for this belief is that thallium-salts, which produce endocrine disturbance, also cause baldness. There is no endocrine therapy that has proved to be definitely of use in any form of baldness, with the possible exception of the diffuse thinning of the hair that occurs in myxedema. For the ordinary forms of baldness, endocrine therapy has not been found useful."

A few years ago, it was discovered as a result of the researches of N. Zuntz, of Berlin, that keratin, a product made from the nails and hoofs of animals, when given internally, is capable of increasing the growth of the hair and wool. This resulted in the active promotion of an internal remedy for baldness. There has been much discussion and the usual newspaper notoriety, and apparently the whole matter simmers down to this: Humagsolan is a lottery; you may win and then again you may not!

Almost the same harsh conclusion must be made regarding any treatment of alopecia—endocrine or otherwise. If the baldness is due solely to dyscrinism, and this has not involved complete follicular atrophy, and the dyscrinism is responsive to the proper therapy, the baldness may be completely cured. But it is necessary to have the right combination of circumstances to succeed.

38. ARTHRITIS

Are the Endocrines Involved?—A Thyroid Aspect—The Calcium Balance—Massive Doses of Parathyroid—Thymus Therapy—Ovarian Arthritis—Non-Specific Protein Therapy.

As ONE of the unsolved problems of medicine, arthritis is being considered from the endocrine aspect in the hope that it might be possible by some sort of endocrine intervention to change the prognosis of this distressing disease.

The subject under discussion here is not rheumatism, which has been considered elsewhere (87), but chronic arthritis with the ultimate picture of arthritis deformans. Quite an extended differentiation of various forms of arthritis is now made, but particular attention will be paid here to the general subject of chronic arthritis from several of the endocrine points of view.

ARE THE ENDOCRINES INVOLVED?—Admitting that there is a nutritional phase to arthritis, the regulators of nutrition ought to have some part to play in both the cause and the cure of the difficulty. Granting also that there is a toxic phase, the endocrines interest us immediately because detoxication is under the control of these organs. Presuming that there is a specialized biochemical irregularity involving the chemistry of lime in the tissues, we recall immediately that this very thing is presided over by one of the more recently appreciated sets of endocrine organs—the parathyroid glands.

The first actual joint pathology in arthritis is a roughening or an infiltrative process that takes place on the bearing surfaces of the joints, as a result of which the joint cannot move smoothly. The grinding and crushing of these roughened areas seem to be the cause of the acute pain. The deposits of calcium and the ultimate immobilization of the joint form a natural defense reaction against this process. Before we can elaborate any logical treatment for arthritis, we must find the cause of this primary roughening and how to control it. In the meantime we must do something for our patients, and we naturally ask ourselves the question, "Does endocrinology offer any hope?"

Arthritis, it is true, is built upon etiological structures such as foci of infection, infectious disease, and alimentary toxemia—all conditions which of themselves stress the endocrines. There is an increasing suspicion that focal infection and other accepted factors in the etiology of arthritis accomplish their dire evil through the glands of internal secretion.

A THYROID ASPECT—There is a very fine dividing line between certain types of chronic rheumatism and some of the minor phases of arthritis deformans. The one merges into the other and, therefore, the fundamental principles that have been borrowed from the writings of Léopold-Lévi, of Paris (87), have a bearing on the subject under discussion here. I think that it may be said without fear of denial that the slowed chemistry of hypothyroidism, and especially maximal degrees of hypothyroidism, are commonly found in patients with arthritis. Further, what is to prevent the infiltration that is so common in hypothyroidism (67) from involving the synovial membranes just as it undoubtedly may involve the lining of the middle-ear (54) or the walls of the bladder (67) among numerous other tissues? Here we have a truly mechanical factor, which occasionally may be the active as well as the predisposing cause of arthritis. If this is the case, obviously the thing to do is to study every case of arthritis most carefully from the standpoint of the thyroid activity, and, if defects are discovered, to correct them as best we can.

THE CALCIUM BALANCE—In recent years the profession has been led to consider the metabolism of lime more closely, largely because of the remarkable developments in our knowledge of the parathyroid glands and their influence on the regulation of calcium chemistry (16). Since certain arthritic patients have a well-defined defect in their calcium metabolism—many of them even having extensive deposits of lime in the joints—it was decided, as a result of some interesting clinical "accidents," to experiment on a number of them to see if the organotherapeutic measures that we have come to depend on to modify disturbances in the calcium balance might not also help the arthritis. The idea appears to be gaining ground that in many cases of rheumatoid arthritis and arthritis deformans one of the important features is a peculiar upset in the chemistry, which has been called "calcium gone wrong."

It happens that lime is found in the body in two distinct forms: (1) the ordinary lime of the bones and teeth, and (2) a soluble, "ionized" calcium. The latter performs a series of vital detoxicative services in preventing acid protein waste products from doing damage and at the same time assisting the body in the neutralization of other acid by-products such as are found in tuberculosis, which, as we shall see (94), is largely a problem of calcium regulation.

It has not yet been established whether or not calcium "goes wrong" as a result of a defect on the part of the parathyroid glands; the probability is that it is not essentially a manifestation of parathyroid insufficiency. But,

since these little glands regulate the concentration of calcium in the tissues, and are capable of modifying the form of lime that may be fixed in the body itself, or that may be administered as a calcium food, it is interesting to see if they do not have some influence on the improperly located lime in arthritis deformans.

This is not illogical when we recall that a low blood calcium may be increased greatly under the influence of potent parathyroid preparations. For example, I. Greenwald and J. Gross, of New York (*Jour. Biol. Chem.,* Nov., 1925, lxvi, p. 217), report that, in tests on animals practically deprived of calcium in the food, the calcium content of the blood was increased by the use of the parathyroid hormone. These authors conclude that this increase must have been at the expense of certain tissues, and, since the increased excretion of calcium was regularly accompanied by an approximately equivalent increase in the excretion of phosphorus, they assume that both the calcium and the phosphorus were derived from the bones, since there seems to be no other tissue in the body that could supply the large amounts that were reported to have been lost.

Now, two other most interesting biochemical coincidences lend interest to our prospective empiricism. Several reports in the literature indicate that parathyroid therapy is useful in treating plumbism because it releases the lead that has been fixed in the tissues. (J. C. Aub and D. Hunter, *Quart. Jour. Med.,* Jan., 1927, xx, p. 123.) More recently, in the studies that were carried out at Johns Hopkins Hospital in a series of women who had acquired so-called "radium deposits" from their use of "radium paint," it was found that injections of Parathormone released more of the radio-active material from the tissues, where it had been thought to be irrevocably fixed, than did any other measure or remedy. (F. B. Flinn and S. M. Seidlin, *Bull. Johns Hopkins Hosp.,* Nov., 1929, xlv, p. 269.)

MASSIVE DOSES OF PARATHYROID—Following a suggestion originally made by Bertha van Hoosen, of Chicago, an effort has been made to treat a series of cases of hopeless arthritis deformans with huge doses of parathyroid. The formula, Para-Spleen Fortior,* was used, each tablet of which contains 1 gr. of the true parathyroid desiccation (twenty times the usual unit dosage) plus as much spleen concentrate as possible. The dose of this preparation is one tablet three times a day, which probably is forty times more than what has been considered the average oral dosage of parathyroid extract. This increase was based on the supposition that, if parathyroid substance is given in large enough doses in cases where calcium is deposited abnormally in the joints and elsewhere, the increased affinity of the blood for

lime brought about by the influence of the parathyroid hormone, might be satisfied first at the expense of the lime in these arthritic deposits rather than from that of the bones.

A number of physicians who carried out this treatment in several scores of patients, found that the first reaction was usually an encouraging one. Several symptomatic improvements were noticed: The first had to do with the pain, the second with the mobility, and the third with the actual size and appearance of those joints that could be seen. Undoubtedly, there is an increase in the amount of lime lost by these patients; but, despite this chemical confirmation of our clinical suspicions, the tendency toward the deposition of lime in the joints does not seem to be definitely controlled. In other words, we are confronted with a development in therapy which, although symptomatically interesting and worth while so far as the patient's immediate comfort is concerned, is still fundamentally limited in its possibilities as a curative measure.

This idea of parathyroid therapy in ultimate arthritis is now receiving attention abroad. For example, in the Paris correspondence to the *Journal of the American Medical Association* (Feb. 28, 1931, xcvi, p. 702), the following appears:

"For several years Léopold-Lévi and Henri de Rothschild have called attention to the rôle of the thyroid secretion in arthritis deformans, and they have introduced a form of treatment with powdered thyroid substance, which has often given good results. At present, extracts of parathyroid glands are being tried, although the parathyroid glands are supposed to have an action rather antagonistic to that of the thyroid. Weissenbach, Fraujon, Perlès, and Seidmann have announced the results that they have secured over a period of more than a year in a dozen cases of chronic arthritis deformans in which they used parathyroid therapy subcutaneously in successive and repeated series, with a dosage of from 1 to 2 cc. daily. In general, an immediate local and painful reaction follows the injection, which produces marked relief, a quieting of the pain symptoms, and a frank functional amelioration, which persists for several hours. The improvement appears to be more stable if a sufficient number of injections have been given. When the treatment is stopped, one often observes recurrences of the articular symptoms. In general, the final results are satisfactory. The joints become supple and the general condition improves. However, one must watch for signs of intolerance. The authors are unable to reach a definite conclusion with regard to the nature of the action of this glandular extract."

Undoubtedly, the future will disclose a number of diagnostic developments that have not yet been uncovered. We shall learn, perhaps, that allergy or the protein waste products of certain alimentary parasites are capable of so sensitizing the detoxicating mechanism that it fails to produce the proper

kind of metabolic end-products, with the result that some intermediate substances are permitted to enter the blood stream and disorganize the joint tissues which, for certain other reasons, infective and endocrine, have been rendered peculiarly susceptible to the detrimental influences of these products.

THYMUS THERAPY—In 1911 Philip W. Nathan, of New York, discovered that thymus extract, given in doses ranging from 15 to 45 gr. a day, seemed to cause symptomatic betterment in a number of cases of chronic arthritis. According to this worker, rest, a nutritive diet, and thymus medication frequently relieve the more active symptoms in the milder cases. In severe and intractable cases, this treatment, continued for months, was followed by encouraging results, many hopeless, bedridden patients being markedly benefited. Nathan believes that, if the thymus extract is taken conscientiously for a long time with judicious treatment, marked improvement, if not perfect cure, can be expected.

When the opportunity came to me to prepare certain endocrine formulas, several friends were anxious to use adrenal support as a tonic in a number of run-down cases with chronic arthritis. This was done for the very good reason outlined in a number of places in this book—that patients who are toxic, depleted, and asthenic are good subjects for general endocrine stimulation. And this is just the picture so often found in patients with arthritis. Many of the reports were good. This general arousing of the cellular chemistry made a change for the better in a number of cases of arthritis. On hearing of Nathan's work, it was suggested that these two ideas might properly be combined. So there was prepared the formula known as Thymus-Spermin Co.,* which consisted of equal parts of Adreno-Spermin Co.* and a concentrate from the neck thymus of calves. This formula has been in use for more than twelve years, and, although there are many reports indicating that its use was followed by symptomatic improvement, there are others that infer that it has no direct or specific antiarthritic effect. Some physicians reported that it was a great advance over either thymus extract or the adrenal combination alone, while others thought that the addition of thymus was no improvement. As a matter of fact, there are very wide differences between cases of arthritis, just as the cellular responsiveness of these patients varies greatly.

In 1920 a series of thirty cases of arthritis was treated with this formula over periods ranging from two to seven months, the length of time depending upon the response of the patients. There was benefit in about 40 per cent., and it was noticeable that all the improved cases were chronically toxic and depleted. When there was improvement of a general nature with increased

euphoria, local benefit was more likely. Invariably the joint symptoms were better in proportion to the general improvement. The first feature to be benefited was the pain, next the tenderness, then the mobility, and, last and least, the deformity.

OVARIAN ARTHRITIS—Without a doubt, certain women, especially at the menopause, undergo a series of metabolic changes that make them especially susceptible not only to rheumatism, but to arthritis as well, as is outlined in Chapter 87. Whether this is essentially a thyroid problem, such as has been referred to previously, or whether it is connected with the parathyroid functions, is not yet determined; nevertheless, all three of the measures previously outlined are worthy of consideration in menopausal arthritis. To this broad idea is added the fundamental suggestion that when there is a disturbed endocrine function due to a development that cannot be avoided, an attempt should be made to limit the extent of this disturbance even though it is obviously impossible to avoid the ultimate outcome. In other words, since a woman at the change of life happens to be particularly susceptible to arthritic changes, the inevitable endocrine imbalance *of the change itself* should be lessened as much as possible, in addition to treating the joints. This should be done regardless of how few symptoms may be noticed, if only for the reason that it will give certain of the endocrines a better opportunity to perform some of their duties, which obviously are defective also. This means that menopausal patients with arthritis need to be treated for the menopause (80) as well as for any other condition that may be present. None of the measures suggested here interfere in the slightest with the customary pluriglandular therapy of menopausal upsets.

NON-SPECIFIC PROTEIN THERAPY—It happens that a rather interesting development in the treatment of chronic arthritis by means of non-specific proteins is in process of perfection. Obviously, any good attributable to such treatment comes from the reaction of the body to the protein itself. The consensus is that these substances brought into the circulation as a result of the reaction to injections of non-specific proteins are, indeed, endocrine substances. I am in touch with several physicians who, having discovered prospects of benefit from non-specific protein therapy in arthritis, have combined one or another of the foregoing endocrine measures with some injections of milk protein such as Aolan, Lactigen, etc. There can be no reasonable objection against attempting to arouse beneficial responses on the part of the body in more than one way at a time. The subject of non-specific protein therapy is given further consideration in the Appendix (105).

39. ASTHMA

Bronchial Asthma—Cardiac Asthma—Idiopathic Asthma—Asthma and Eosinophilia—Thymic Asthma.

ASTHMA IS a type of dyspnea that is both a symptom and a disease, and too often the respiratory symptom is considered as a fundamental disease when in reality it is only a symptomatic expression of a far deeper, hidden pathology.

BRONCHIAL ASTHMA, so-called, is a syndrome of a recurrent nature that manifests itself in periodic or paroxysmal attacks of dyspnea of differing origin and varying severity, between which the patient is apparently well. In other forms of asthma, to be discussed briefly later, the typical wheezy and difficult breathing is more or less continuous.

Many cases labeled "bronchial asthma" are really protein sensitization, usually of bacterial origin, though other forms of food and pollen sensitization commonly enter into the etiology. Many authors classify the causes of asthma as either extrinsic or intrinsic. Both of these are either hereditary or acquired, but probably there is an inheritance underlying the susceptibility to asthma—an endocrinopathic inheritance.

The intrinsic causes of asthma are less frequent but more serious, such as cardiac, bacterial, and toxic. Two forms of essentially endocrine asthma will be discussed: the pituitary and the thymus types, the latter being a classical endocrine disorder.

CARDIAC ASTHMA—Besides the symptomatic use of adrenalin, there is nothing that can be done from an endocrine standpoint in the regulation of asthma of cardiac or cardiorenal origin. The development of heart-muscle therapy, based largely on the work of Haberlandt and other German workers (12), has enabled us to increase the physiological efficacy of heart muscle that has been degenerating (myocarditis). The administration of Myocardin* has given symptomatic benefit in a number of serious heart conditions, including a few cases in which cardiac asthma had developed. It cannot be said, however, that this extract produces any permanent influence on the degenerative changes in the muscle; therefore, it cannot be considered as a true remedial agent in cardiac asthma. We shall have to depend on the nitrites and other accepted symptomatic treatment. Still, Myocardin is worthy of consideration, especially in view of the facts that it never causes any detrimental reaction and that it may occasionally give the patient some symptomatic benefit.

IDIOPATHIC ASTHMA—When asthma is coincidental with infections such as bronchitis, bronchiectasis, tuberculosis, etc., it seems that nothing can be done from the standpoint of endocrinology. In such cases there is probably a manifestation of an anaphylactic reaction to the bacterial protein waste products that are being produced and absorbed in excess.

In the so-called idiopathic type of asthma, there is no such definite infective basis, and the suggestion has been made that this condition may be an indirect response to an endocrine upset. A few years ago, F. C. Warfel, of Indianapolis, reported some findings connecting asthma with pituitary dysfunction. In view of the fact that an attempt was being made at the time to modify the accepted symptomatic organotherapy of asthma (with adrenalin or epinephrine) by the addition of posterior pituitary solution, a special study was made of asthma from the endocrine standpoint.

A number of cases of bronchial asthma in the Indianapolis City Hospital were given 10 gr. a day (2½ gr., q.i.d.) of anterior pituitary substance. Improvement was noted in several within the first forty-eight hours and was continued in some instances for two months or more. The expectoration was decreased, dyspnea disappeared, and the results were generally encouraging. Based on Warfel's suggestion, an attempt was made to treat a series of cases of this type of asthma with an adrenal-anterior-pituitary combination. The adrenal ingredient was added to this formula because muscular atonicity and asthenia, such as one expects in hypoadrenia, might properly be treated coincidentally. The combination known as Adreno-Hypophysis Co.* has advantages over anterior pituitary substance alone.

There is a somewhat similar solution for hypodermic use in asthma, but, while the foregoing formula represents *anterior* pituitary plus total adrenal substance, the solution is a combination of the *posterior* pituitary principle and epinephrine (1:1000). Attention has been called to the interesting fact that, although pituitrin may give some symptomatic help in asthma comparable with adrenalin, it is not so effective. When the two hormones are combined, however, less adrenalin is needed and the symptomatic improvement lasts longer—sometimes twice or three times as long. Some time after this position had been taken, it was agreed (*Therap. Notes,* Feb.-March, 1920, xxvii, p. 14) that

"Very satisfactory and immediate results can be obtained in the treatment of asthma by the subcutaneous injection of either adrenalin or pituitary extract, or, still better, by a mixture of the two substances."

In the years that have passed, many asthmatic patients have been treated along these lines; and, while there is still no dependable remedy for idiopathic

asthma, it is certain that in many cases the oral administration of an adrenal-anterior-pituitary combination has lessened the need for the injections. Old cases that had been forced to take as much as an ounce of adrenalin solution (1:1000) daily have been able to reduce this enormous dosage by one-half or more. True, the asthmatic diathesis usually continues, but, although the patients are not cured, it is more convenient and less expensive to reduce the need for the hypodermic medication by the associated oral organotherapy.

As the influence of the pituitary on nutrition and endocrine regulation became appreciated, it was hoped that we would learn something more definite about these empirical clinical experiences, but so far no explanation has been found. However, many who once objected to the crass unscience of this method, having become so thoroughly converted to other endocrine measures, no longer express themselves quite so harshly as they once did. Maximilian Kern, the Chicago neurologist (*Am. Med.*, June, 1925, xx, p. 341), states:

"Sufficient has been said to show that the endocrine factor cannot be ignored with impunity in the study of the etiology of asthma. Indeed, it is not too much to maintain that the endocrine factor may be responsible for conditions that have an intimate relation to asthmatic attacks. . . . Without any desire to become one-sided or to overlook the scientific work on other routes, endocrinology presents probabilities that should be thoroughly investigated by the sagacious clinician seeking to benefit asthma sufferers."

The fundamental principle that prompts the consideration of the endocrine aspect of all problem patients applies very definitely here. It will be found that many asthmatics who depend to a heart-breaking degree on epinephrine for even limited comfort, receive additional benefit from the regulation of any endocrine disorders that may be present, and are thereby freed from the necessity of taking so much of the drug.

ASTHMA AND EOSINOPHILIA—In recent years the coincidental finding of an increase in the proportion of eosinophilic neutrophiles in the white cell counts of asthmatic patients has been noted more frequently, and in several text-books eosinophilia is given as a usual finding in asthma.

The coincidence of eosinophilia and certain dermatoses has been mentioned in Chapter 50, and a new measure has been set forth as of prospective service in these cases—a solution of the active principles of the spleen. It happens that the Munich workers, to whom we are indebted for this new idea in spleen therapy (21), found that asthma also has been benefited following injections of spleen extract, provided there is a coincident eosinophilia. (Leo von Zumbusch, *Urol. and Cutan. Rev.*, Dec., 1927, xxxi, p. 750.)

A number of cases of idiopathic asthma in which the eosinophile count has ranged from 5 to 15 per cent. have responded well to injections of Splenocrin.*

The procedure is identical with that suggested in dermatologic practice: First, connect the manifestation with a high eosinophile count; then give a preliminary intragluteal injection of 2 cc. of Splenocrin Solution to determine the patient's tolerance, and the next day or the day after give from 10 to 18 cc. intragluteally in one or two injections at the same time.

Occasionally there is a prompt and unexpected improvement. When this occurs, a second large dose (as much as 20 cc.) may be given at weekly intervals for several weeks. The proportion of good results is not large, probably because asthma is rarely a simple condition.

THYMIC ASTHMA is a very definite and disconcerting syndrome, occurring usually in children. Although the cause is commonly overlooked, it is easily diagnosed and quite satisfactorily treated. The thymus, still not definitely classified as a gland of internal secretion, is a lymphatic structure that certainly manifests close endocrine connections (23). When, as happens quite rarely, the thymus gland is especially enlarged, the actual pressure causes a difficulty in breathing known as thymic stridor or asthma.

The available information on this subject deals chiefly with diagnosis and treatment, and does not attribute this condition to a specific cause. Naturally, thymic asthma is more liable to occur in the lymphatic type of child, discussed elsewhere (93). It will be found that, in these cases, there are practically always other evidences of endocrine upset, such as growth dystrophies.

In the last twenty years, I have seen several cases of thymic asthma in boys, but none in girls, although I know of no reason why it should not occur with equal frequency in both sexes. In all these cases, there was a considerably reduced intelligence quotient, and the patients were not passing in their school work. Antiasthmatic treatment of various types had been given to all, with symptomatic benefit in some and none in others. The discovery of a well-defined thymic shadow led the way to X-ray therapy, and two or three applications of suitable dosage sufficed to shrink the hyperplastic organ so that there was spectacular improvement in the breathing. I have followed some of these patients for several years, and in every one there has been prompt and lasting improvement in the general health and intelligence, although none of them had been especially retarded mentally—they were just slow in their studies.

A warning should be given here regarding the immediate response to X-ray therapy of the thymus. Sometimes following suitably heavy exposure there is a very decided toxemia with corresponding depletion. In such cases, the patient should be put to bed or at least kept at home for the first day or two after each X-ray exposure.

40. BLOOD DISORDERS

Adrenal Anemia—Hypothyroidism—Chlorosis—Erythremia—Leukemia —Pernicious Anemia—Secondary Anemia.

THE PRODUCTION of the blood-cells, both red and white, and the maintenance of the hemoglobin percentage and color-index ratio undoubtedly are influenced in a decided way by the endocrine glands in health as well as in disease.

ADRENAL ANEMIA—The picture of Addison's disease, already outlined (35), invariably includes a blood dyscrasia. As a result of his studies of ultimate adrenal disease, the famous physician of Guy's Hospital was led to a more careful consideration of various types of anemia, and his name was given to what we now call pernicious anemia—Addison's anemia. There is, however, a great difference between the secondary anemia of addisonism and the primary addisonian anemia.

Hypoadrenia of maximum degree causes serious anemia, for which neither hematinic nor liver therapy is very useful unless an effective adrenal therapy is given with it. For this purpose the adrenal cortex hormone, Adreno-Cortin,* may be injected intramuscularly—1 or 2 cc. daily.

J. Pal, of Vienna, believes that adrenal cortex therapy is directly capable of facilitating blood regeneration. The following is translated from his paper (*Wien. klin. Wchnschr.,* Aug. 23, 1928, xli, p. 1216):

"In my investigations I employed various substances. I would only say here that with oral administration of adrenal cortex I obtained splendid results in various diseases so far as regeneration of the red blood-corpuscles is concerned. Out of twenty-five cases discharged from the hospital, I am able to record seventeen positive results. . . . According to Stephan, by means of injection of extract of adrenal cortex the number of red cells, after a temporary drop, can be raised for hours—an effect that may also be produced in pernicious anemia and carcinoma."

HYPOTHYROIDISM—Other major types of dyscrinism such as hypothyroidism, for example, are always found associated with a more or less serious change in the blood findings, if only because of the inevitably increased toxemia and the cellular infiltration resulting from thyroid insufficiency, which automatically involves the hemopoietic organs. This explains why there are many reports in the literature telling of the improvement in the blood-picture that accompanied other changes for the better, following indicated thyroid therapy. From this, we conclude that every case of secondary anemia deserves consideration from the endocrine standpoint.

The blood-picture of marked hypothyroidism shows that hemopoiesis is interfered with, that the vital hemoglobin is reduced, and that the defenses of the body are lowered, for the white cells are reduced in number and the proportion of "fighting cells" (phagocytes) is commonly low in comparison with other types. Thyroid therapy is not a remedy for anemia, but it is a specific for a condition that often underlies anemia. Both conditions must be treated together.

CHLOROSIS—Again, anemia is often found in connection with a serious derangement involving the ovarian function. In fact, there is a special form of hemopoietic malnutrition known as chlorosis, which is uniformly a disease of girls and young women occurring usually at puberty or soon after. It is almost invariably associated with the endocrine stress that commonly shows itself at this time in such other manifestations as amenorrhea, goitre, or obesity.

Chlorosis is more definitely a nutritional disorder than an anemia, for usually the red cell count is not far below normal. The toxemia and malnutrition are always accompanied with a comparatively low hemoglobin index, and the typical, peculiar pallor of the skin disappears as the hemoglobin percentage is reestablished, provided that the underlying endocrine imbalance is controlled. The treatment, which is virtually specific, is that recommended for dysovarism plus anemia. Adreno-Ovarian Co.* has been used in a number of cases as an effective tonic regulator of the endocrine functions most usually involved.

Ordinarily, hematinics fail to give the service expected, probably because they are not directed at the evident underlying difficulty. As a matter of fact, since the ovarian aspect of chlorosis has been appreciated, this disease is becoming increasingly rare.

In all these anemias, a hemopoietic liver product is indicated in addition to the other treatment; when used alone in the treatment of chlorosis, it usually fails.

ERYTHREMIA—This rare condition has several names—Vaquez' disease, polycythemia, splenomegalic polycythemia, and Osler's disease. Because its antitheses are influenced by organotherapy (see anemia, pernicious anemia, etc.), attention has been paid to the possibilities of this treatment in erythremia.

The unusually high red cell count pathognomonic of erythremia is due to an excessive erythroblastic function presumably in the bone-marrow itself, though the spleen also is involved. Two hypotheses regarding its origin

involve endocrine matters, though not in a very clinically helpful way. First it is suggested that erythremia is akin to leukemia and really "a form of malignancy." The second hypothesis is that the disease is a form of hyperhemopoiesis due to imbalance in the regulation of the bone-marrow functions, which are believed to be under hormone control.

Treatment includes X-ray to the hemopoietic centers and the spleen, and organotherapy for any defective function, especially of the liver. Phenylhydrazine is still the best direct therapy.

LEUKEMIA—Three facts have led to the belief that leukemia is a semiendocrine problem: (1) the usual involvement of the spleen and the coincidental presumption that it is a gland of internal secretion; (2) occasionally one finds that the thymus is "resurrected" from the inert, atrophic rest that is normal in adults; and (3) the peculiar similarity between certain manifestations of both myelogenous and lymphatic leukemia and hyperthyroidism. The latter is frequently associated with a moderate lymphocytosis, and in acute leukemia there may be an increase in the B.M.R. Add to this the temporary clinical improvement that follows X-ray therapy of the spleen, and we have enough reasons to feel that the various forms of leukemia may indeed be endocrine manifestations.

Whether this is true or not, organotherapy as yet is of no value in the control of leukemia. Spleen extract has no such effect in this disease as it has in splenomegaly (89). Because of this fact, certain French authors writing from Cochin-China, where spleen diseases are unusually common, have suggested that spleen therapy may be used as a supplementary differential diagnostic measure in these two conditions.

Although liver therapy is effective as a hemopoietic in leukemia, it is disappointing; for the results, while acceptable, are not comparable with those obtained in the anemias, and the white count is not lessened.

The leukemias—myeloid and lymphatic, acute and chronic—remain medical mysteries, with cause still unknown, progress most variable, and outcome always fatal. At present the best therapeutic prospect is arsenic in the form of the solution of potassium arsenite.

PERNICIOUS ANEMIA—The primary form of anemia originally described by Addison and now usually known as pernicious anemia, is one of the conquests of modern organotherapy. This most resistant of all medical problems responds in an amazing way to liver feeding.

This great therapeutic advance came about when Minot, Murphy, and their associates at Harvard University utilized the fact, demonstrated by

G. H. Whipple and associates at the University of California more than five years before (*Am. Jour. Physiol.*, 1918, xlv, p. 573; 1920, liii, p. 151), that liver feeding causes a rapid regeneration of blood in dogs with maximum degrees of anemia produced by repeated bleedings.

(In going through the literature it seems that credit will have to be given to Pietro Castellino, of the University of Naples, for priority in suggesting liver therapy in anemia. At least, in an article published in *Nuova Vita* for December 15, 1912, he reports good experiences from such therapy. These were later confirmed by Tommasi.)

At first (1926), the Harvard workers used fresh or slightly cooked calves' liver, and for a time quite a liver-eating fad swept over the country. It was not long, however, until a water-soluble liver extract representing one part of the finished product to from thirty-seven to forty-five parts of fresh liver was available. The very real difficulty of liver feeding was fully overcome, for half a pound of beef liver daily, raw or cooked, was not only quite monotonous, but to many it was actually disgusting.

In 1927 I learned that in the Multnomah County Hospital in Portland, Oregon, liver therapy was being given in an extended way to serious anemias not of the true pernicious type, and that O. Larsell and several other workers there were making a special nuclein extract from the liver to supplement their own water-soluble liver extract. For ten years I had been emphasizing the supplementary value of sodium nucleate or nucleic acid in anemia, goitre, etc., so I began to use and to recommend a product that contained not only a proper dose of highly concentrated hemopoietic liver extract but an unusually large dose of sodium nucleate.

(Nucleic acid is really an organotherapeutic product, for, although it is now produced from yeast, it was originally made from the thymus. It contains a higher proportion of organic phosphorus than any other conveniently available substance. It is also one of the most marked leukocytogenetic remedies known.)

In view of the reports emphasizing the synergistic value of iron with the liver hemopoietin (13), I decided to substitute iron nucleate for the previously used sodium salt. This product, known as Heparnucleate,* is undoubtedly a valuable measure in the treatment of all forms of anemia.

As to dosage, it has been found that 4.5 Gm. of this compound extract, *i.e.*, 3.5 Gm. of hemopoietin (equal to about 175 Gm. of fresh liver), given each day, is capable of causing an average increase of 100,000 red cells a day. It seems that this measure delivers essential materials to the organism and does not act in the catalytic manner expected of hormones, although some

German writers have expressed the thought that this method is truly hormonic in its action. At all events, it is good policy to "pile up" these materials so as to be sure to have available all that can be used. A minimum of two tubes (9 Gm.) of Heparnucleate is used daily during the first week or two, then reduced to one a day. The powder is worked up in plain water, milk, orange juice, or soup (not hot), and is usually taken just before meals, as digestion exerts no detrimental effect upon it.

The most spectacular change in the blood figure following the use of Heparnucleate was seen in an old man with a blood-count of only 900,000. (The figure was verified because it was so low.) After one month of treatment (24 doses) the r.b.c. was 3,800,000, and there was a coincidental gain in weight of 18 pounds. It has been noted frequently that the lower the r.b.c. at the start, the better the prospect of a large increase from this treatment.

An early misunderstanding led several writers to the conclusion that liver therapy was a truly curative measure in pernicious anemia. Read, for example, the quotation from an editorial in the *Lancet* (see page 60) in which this remedy is called "so simple and yet so specific a cure for a hopeless condition." Unfortunately these cases are not cured.

However, many a case of ultimate pernicious anemia has been arrested by liver therapy. The blood-picture has been revolutionized and the general condition decidedly improved. But these patients will relapse if the liver is discontinued for any length of time. In fact, my own moderately extensive experience has led me to conclude that liver therapy in serious anemias can be used as a differential diagnostic measure. Virtually all forms of anemia improve remarkably under liver therapy, as we shall see; but it must be continued in the pernicious cases, for the effects soon wane and treatment must be started again and prolonged almost indefinitely. (Incidentally, I have found that the ingestion of only half a pound of raw liver once a week adds remarkably to the response to liver extract when its effect is beginning to wear off.) On the other hand, the improvement in the secondary anemias usually continues after the liver therapy is stopped. It is wise, in these cases to reduce the dose gradually after the blood-count has been normal for two consecutive weekly counts.

A word must be added here about the effect of liver therapy on the neural aspect of pernicious anemia. It is evident that this treatment has certain limitations as regards its influence on the cord changes. It is hemopoietic, not regenerative. The present opinion is that liver therapy makes very little difference to the ultimate nerve changes. It is true, however, that the improvement in the nutrition of the nerve tissues involved may cause some

benefit, and several writers have reported improvement in the purely nervous characteristics of the disease. For instance, Richard S. Moynan, of Columbus, Ohio (*Am. Med.*, Dec., 1929, xxxv, p. 787), submits the following:

"A colored woman, gravely ill with pernicious anemia with nervous and mental symptoms, was treated with liver extract and fresh cooked liver without the use of hydrochloric acid. Mental recovery and practical physical restoration resulted, but achlorhydria and some nervous symptoms were unimproved."

Again, in the *Southern Medical Journal* (Dec., 1927, xx, p. 926), E. M. McPeak, of San Antonio, and DeWitt Neighbors, of Fort Worth, Texas, conclude:

"In addition to the improvement in the blood-picture, there has been striking improvement in the general appearance, sense of well-being, and neurological symptoms."

Another more recent development in the organotherapy of pernicious anemia is the discovery by C. C. Sturgis and R. Isaacs, at the University of Michigan (*Jour. Am. Med. Assn.*, Sept. 7, 1929, xciii, p. 747), that the feeding of desiccated hog's stomach to these patients causes a remarkable reticulocytosis. The original product known as Ventriculin is somewhat less expensive, gram for gram, than liver extract, but the effective dose is considerably larger. Comparisons have been made between the clinical effects of these two types of products, and there seems to be no advantage of the hog-stomach desiccation over liver extract.

Since achylia gastrica is pathognomonic of pernicious anemia, and is therefore a matter to be routinely cared for in these cases, the reader will be interested in the consideration of this subject also (53). Myogestin,* a muscle-digest developed recently, is a beneficial supplementary measure causing improvement in both the digestion and blood in pernicious anemia.

SECONDARY ANEMIA—Because Minot and Murphy conducted their clinical experiments in cases of true pernicious anemia, liver feeding for some time was confined to this type of anemia. Several references may be found in the literature suggesting that liver treatment is indicated only in the pernicious type of anemia. The following from the *Journal of the American Medical Association* (June 16, 1928, xc, p. 1968) is illustrative:

"Up to the present time, the ordinary liver extracts employed for the treatment of pernicious anemia have not been found to exercise any beneficial effect in other types of anemia."

This opinion has been found to be fallacious, as will be confirmed later; but, before the error was demonstrated, there was some criticism of those,

who, like myself, insisted that liver therapy should be beneficial in all serious anemias. It was not merely a few early and stimulating experiences, accurately confirmed by many blood findings, that convinced me of its efficacy in other anemias; but it was a very natural deduction from the report of Whipple, whose experimental work was on a *secondary* form of anemia, such as that which follows repeated bleedings.

It would have been a great misfortune if it had been true, as was originally suggested, that the benefits of liver therapy were limited to pernicious anemia. Many thousands of cases of every description have been treated with liver therapy, including chronic anemias accompanying conditions requiring operation, the true seriousness of which was realized when the routine preoperative blood-count showed that an anesthetic should not be given. In such cases, I have given Heparnucleate* for from one to two weeks with an increase in the red cells as great as one million, and with a satisfactory outcome, the surgery being done without incident.

In 1928, an interesting report came from the University of Oregon (*Jour. Am. Med. Assn.*, Jan. 14, 1928, xc, p. 75), in which the figures and charts emphasized the fact that outstanding benefit had been secured from the use of liver therapy in other forms of anemia than the pernicious type, and also in anemias of childhood. For instance, a 2-year-old girl, anemic from birth, was given 3 Gm. daily for seven weeks. The hemoglobin was raised from 28 to 98 per cent. and the red blood-count from 3,400,000 to 5,680,000. Again, in a 13-year-old girl with secondary anemia, the same dose for only four weeks raised the hemoglobin from 72 to 96 per cent. and the red blood-count from 3,920,000 to 5,740,000. These Portland workers, Olof Larsell, N. W. Jones, B. I. Phillips, and H. T. Nokes, remark:

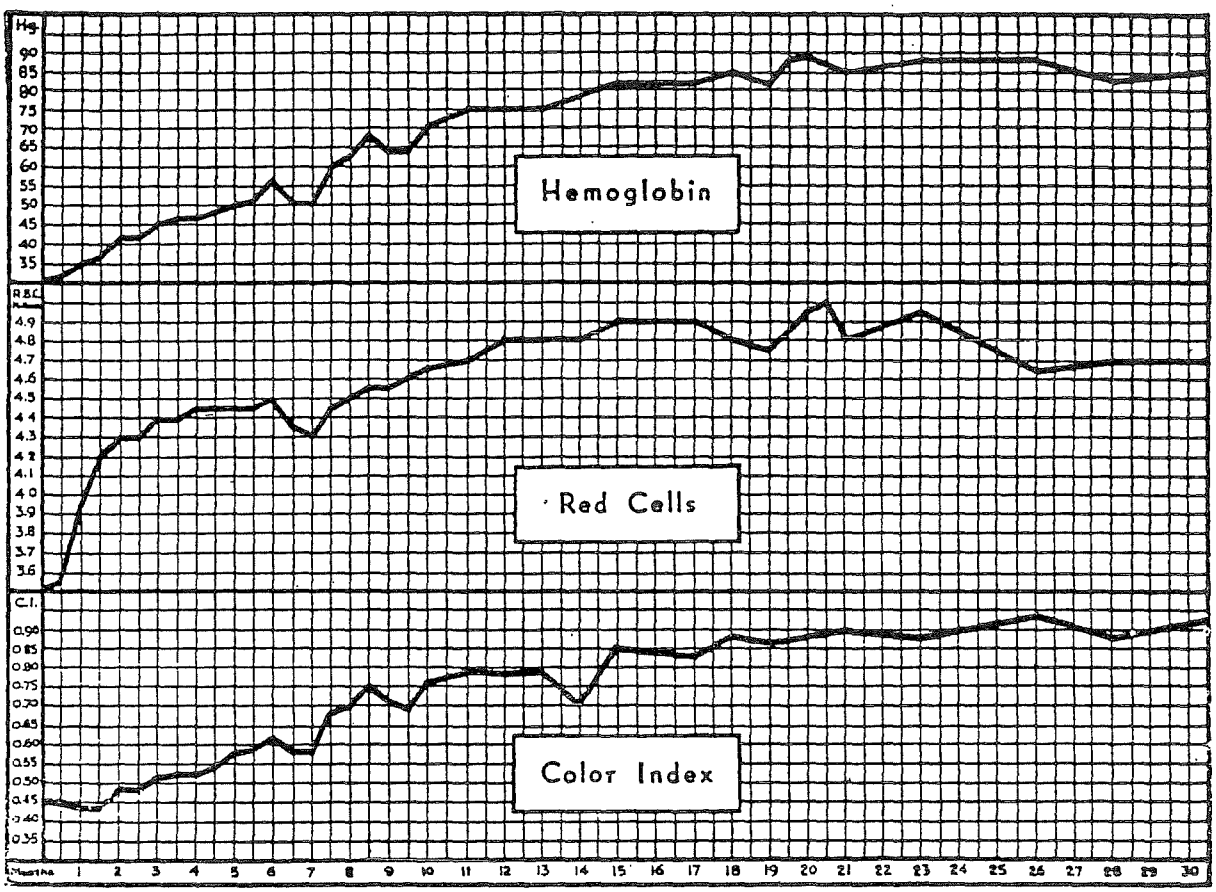
"The conclusion appears warranted that nucleoprotein obtained from beef liver serves as a hematopoietic stimulant. Since separated nuclein from the blood of fowls, and nucleic acids from the same source, are also effective in stimulating hematopoiesis in both experimental animals and anemic human beings, as previously reported, it may prove that the nucleic acid element of the nucleoprotein is the active agent. We have some evidence, however, that nucleoprotein administered with the sodium salts of nucleic acids has a more marked effect in hematopoietic stimulation than either of these alone."

In a second paper published after two more years of experience (*Ann. Int. Med.*, Jan., 1929, ii, p. 603), these same workers confirm their impression that nuclear extractives (nucleic acid, sodium nucleate, etc.) add to the hemopoietic value of liver feeding. For example, they say:

"Those patients who had suffered an acute anemia from hemorrhage, from an acute and transitory infection, or even in certain instances in which the

cause has not been recognized have shown quite as dramatic a response to treatment as any person with pernicious anemia. . . . The same statement may be made in regard to patients with anemia due to uterine fibroids, hyperplastic sinusitis, etc. This point is stressed because there is now a wide-spread suspicion that the use of liver or its extractives holds a certain specificity for pernicious anemia, and that persons suffering from secondary anemias are unimproved by their use. This suspicion is wholly at variance with our experience."

It is not often that one can get a clinical report with as many as sixty-one blood-counts taken at biweekly intervals. But a professional man in Oakland, California, gave himself liver therapy and submitted a list of figures that are charted here.



In the accompanying communication, the doctor gave some additional information and made the comment that

"The Heparnucleate* is a great stimulant to me when I am overworked or not getting enough sleep. It acts in my case as a marked 'pick-up.' So far I have not had a single case that has not shown improvement after taking it."

Particular benefit has come from the use of liver therapy in anemia due to menorrhagia, and, although the menorrhagia itself requires treatment

(80), the hemopoietic value of this formula is often spectacular. One of the numerous reports in the literature that emphasize the value of liver therapy in secondary anemia is that of L. M. Flewelling, of Glendale, California (*Med. Herald,* Oct., 1929, xlviii, p. 294), from which this statement is taken:

"The use of liver therapy has been heralded as a specific treatment for pernicious anemia, and justly so; but we believe that liver feeding is just as potent in severe secondary anemias. Indeed, it has been proved clinically. It has been demonstrated in scores of patients with secondary anemia resulting from various causes, including surgical convalescence, the menopause, and numerous infections."

To substantiate these opinions, Flewelling reports the case of a patient whose hemoglobin was 42 per cent. and whose blood-count was 3,690,000. She was in the menopause, had been flooding for several months, and was in a very depleted state when she came for treatment. She was put to bed and given 4.5 Gm. of Heparnucleate daily. The results were prompt and gratifying. Of course, the blood-count dropped for a time at the heavy menstrual periods, but the improvement was steady. After four and one-half months of treatment the hemoglobin was 86 per cent. and the r.b.c. was 5,500,000. For six weeks following the cessation of treatment both figures remained normal.

It may be added in conclusion that the best results from this treatment are seen after the first two weeks, and in those cases in which the blood findings are lowest.

The decisive effects of oral liver products have interfered somewhat with attempts to perfect similar remedies for hypodermic administration. However, products of this nature have been prepared (see page 131). The injectable liver extracts, such as Hepatopson or Heparhemin,* practically always are recommended to supplement oral therapy with a corresponding product.

In an article in the *Journal of the American Medical Association* (April 11, 1931, xcvi, p. 1198), William B. Castle and F. H. Laskey Taylor, of Boston, report that a readily prepared extract of liver (fraction G), hitherto administered by mouth, is suitable for intravenous injection and is highly potent in pernicious anemia. Maximal reticulocyte responses were obtained from a single intravenous injection of the amount of extract derived from 100 Gm. of liver. One of the patients treated in this manner had failed to respond satisfactorily to the previous oral administration of a similar extract derived from 3000 Gm. of liver given within a period of ten days.

41. BONE DYSTROPHIES

Dwarfism—Fragilitas Ossium—Osteomalacia—Osteoporosis—Paget's Disease—Rickets—Ununited Fractures.

IT IS only within the last ten years that the intimacy of the parathyroid glands and the calcium regulation has been fully realized. This knowledge has necessitated a revision of opinions regarding all dystrophies that involve the osseous system, and has made it possible to intervene effectively in certain bone dystrophies that are associated with hypocalcemia and, usually, with hypoparathyroidism.

DWARFISM—There are three types of dwarfism, one of which is not essentially endocrine in character. Achondroplasia has been considered separately (33), since it, like Hodgkin's disease and leukemia, is commonly supposed to be a disorder of internal secretion, although it really is not.

The two definitely endocrine types of dwarfism are cretinism and the Lorain-Lévi type of hypopituitarism or diminutivism. The former is considered as a childhood endocrinopathy (46) since the shortness of stature is but one feature of the symptom-complex. For convenience, the latter is discussed with the other manifestations of hypopituitarism (83). However, here is one brief quotation from Harvey G. Beck, of the University of Maryland (*Endocrinology,* May-June, 1926, x, p. 327):

"In pituitary dwarfism in which skeletal growth was arrested at an earlier age than normal puberty and the epiphyses are still ununited, anterior pituitary feeding will frequently cause a renewal of skeletal growth even after cessation for a number of years. . . . McGraw observed that in cretinoid dwarfs, growth is much accelerated by administering anterior pituitary lobe extract in addition to thyroid."

Suffice it to say that thyroid therapy makes a cretin grow like a weed, and contributes something very vital to those of short stature, provided that bone growth is not impossible, as evidenced by closure of the epiphyses.

FRAGILITAS OSSIUM—A personal clinical experience makes a much greater impression upon one than anything that is read. Unusual fragility of the bones renders them liable to many fractures, some from activity that is so normal that they have been designated "spontaneous fractures." My comments on the bone dystrophy known as "fragilitas ossium" consist largely of a clinical experience that is hard to forget.

My story is about a little girl, between 4 and 5 years old, who had had seventeen fractures at various times and in various places. I recommended Para-Spleen Co.* and the usual remineralizing procedure (100). After

several months, the mother brought the child to me with the report that she had had no more fractures. She then told how her sister with her little boy came to Long Beach to stay with them for a while. One day the two cousins, about the same age, were playing on the front porch. Accidentally the girl was pushed off and fell about two feet. She lay still a moment, felt herself all over very carefully, then got up and ran to her mother, crying, "Oh, Mammie, Mammie! Johnny pushed me off the porch and I haven't broken anything!"

Several other cases have been encountered, and it appears that indicated regulative organotherapy for the control of some coincident developmental dystrophy is helpful. The younger the patient, the better the prospect of benefit.

OSTEOMALACIA—Softening of the bones with gradual deformity resulting therefrom is a disease entity known in antiquity. Strangely enough, osteomalacia for years was considered chiefly as a dystrophy involving the ovaries, a view that seemed to be confirmed by reports of improvement in the bone condition following ovariectomy. Its greater frequency in women and the fact that it often began during pregnancy served to connect it with the ovaries. However, with the newer knowledge of the importance of the parathyroid regulation of calcium metabolism, the possibilities of parathyroid therapy are now beginning to be realized in the treatment of osteomalacia.

While conducting an autopsy of a woman, age fifty-nine, who had died of osteomalacia that had begun thirty-one years before, Fritz Kerl, of Göttingen (*Deutsch. med. Wchnschr.*, July 31, 1925, li, p. 1271), found a considerable parathyroid enlargement, which he believed had occurred in response to increased demands on these glands because of a lack of calcium in the bones. Long before parathyroid therapy was appreciated as it is to-day, F. H. McCrudden and H. L. Fales, of Boston (*Arch. Int. Med.*, March, 1912, ix, p. 273), reported that a complete metabolism experiment of ten days' duration in a case of non-puerperal osteomalacia showed a definite loss of calcium and retention of all other elements. These authors say that the starting-point of the disease can usually, if not always, be traced to a demand for calcium salts.

V. R. Perretti, of Naples (*Riforma med.*, Nov. 7, 1927, xliii, p. 1062), reports osteomalacia in a woman, age forty-six, to whom parathyroid was given by mouth. There were improvement in the calcium metabolism and a general sense of well-being; the pains in the bones subsided and, some time after the treatment, which lasted only a month, the gait of the woman became almost normal.

OSTEOPOROSIS is one of the osseous dystrophies about which we still know very little. Practically all the recent reports refer to the parathyroids as the prospective cause, and osteoporosis is now believed to be a concomitant of hyperparathyroidism or parathyroid tumor (81). Unfortunately, this has not improved the prognosis.

PAGET'S DISEASE—The osseous dystrophy known as osteitis deformans to which the name of its discoverer, Sir James Paget (1877), is usually given, is clearly a form of specialized malnutrition, although the cause is still unknown. We cannot expect to control the changes in the bones of the skull, but eventually it may be possible to modify the underlying dyscrasia and to prevent further malformation.

Probably this disease includes a parathyroid dysfunction resulting in defective calcium fixation. Probably also, like rachitis, the vitamins—especially *D*—will be found helpful. The ionic blood calcium should be studied carefully, and, if the quantity is reduced, a combined therapy consisting of parathyroid, calcium, and vitamin *D* is indicated.

RICKETS—The specific curative and prophylactic effects of vitamin *D* in rickets place this bone dystrophy beyond the necessity of discussing it here. The medical consensus is that rickets is a deficiency disease and that we have solved the problem satisfactorily by the discovery that Ergosterol or the irradiated product, Viosterol, which contain the antirachitic vitamin, supplies the deficiency. A consideration of the vitamins (101) always includes a brief outline of what they do, but we still have much to learn about *how they do it*. When our knowledge is more complete, I believe that we shall find three factors involved in the initiation of the deranged nutritional balance in rachitic children: (1) the endocrines, particularly the parathyroids; (2) the accessory foodstuffs, especially vitamin *D;* and (3) sunshine, or its poor substitute, the ultra-violet ray.

That these factors cooperate in fortifying the infant organism against the calcium defect that is found in rickets, is undoubted; that one is more important than another from a physiological point of view, I firmly believe. In other words, the parathyroids are suggested as the source of the difficulty; vitamin *D* is clearly the best means of modifying it, and sunshine is the great prophylactic element of which our civilization has deprived us.

At present, the vitamin therapy of rickets is as nearly perfect as we can wish for, hence organotherapy is of secondary importance. Despite the value of the current therapy of rachitis and the excellent results obtained from it, it is well to keep the endocrines in mind when considering these children.

Many a rachitic child is an endocrinopath. The rickets is but one manifestation of a nutritional defect. In such cases, of course, the treatment is broadened by recourse to the indicated endocrine encouragement (46).

UNUNITED FRACTURES—As the surgeons have seen how nutritional changes can be brought about by recourse to organotherapy, they have coveted the opportunity to intervene in a similar chemical way in some of the problems that disconcert them. If organotherapy can be used to modify bone growth and nutrition in disease, why not avail oneself of this principle in health, or at least in an apparently normal person whose bone union is not satisfactory? As usual, this idea was applied first in several difficult cases in which fractures had failed to unite for months. The results were surprisingly good, and now it is not at all unusual to resort to organotherapy to hasten callus production, calcification, and the union of fractures. This idea is of particular value in the treatment of fractures in patients whose nutrition is poor and who are not "good subjects" because they have tuberculosis, malnutrition, diatheses, etc. For example, J. Clifford Hoyle, of Cambridge (*Practitioner,* May, 1930, cxxiv, p. 540), concludes that

"Clearly, then, parathyroid treatment may be of benefit in cases of delayed union of fractures—a condition not infrequent in elderly patients."

Still more recently an editorial writer in the *Journal of the American Medical Association* (Feb. 7, 1931, xcvi, p. 443) remarks:

"Just as a lack of parathyroid function appears to exert an inhibiting effect on the rate of healing of fractures, evidence exists showing that, by administering the hormone of this gland, calcification and union are favored. In this case, the striking feature of the result of injecting parathyroid extract is the marked increase in the concentration of calcium in the blood."

A routine followed by several colleagues is as follows: From the time of splinting, as early as possible, give Para-Spleen Co.,* 2 sanitablets t.i.d. for three weeks, then 1, q.i.d. until the patient is discharged. Simultaneously 1 cc. of the solution of the same product is given daily for the first five days, then 1 cc. every other day. In addition, from 7½ to 10 gr. of calcium lactate is given t.i.d. for obvious reasons. Time and again an old ununited fracture has been surprisingly healed by this therapy.

Some intriguing results are being studied in connection with the incidental discovery of markedly increased callus formation following fractures of senile bones. Unusual X-ray shadows, confirmed by autopsy findings, indicate that Adreno-Cortin* exerts a beneficial influence on the knitting of fractures in the aged. This idea is now being developed further.

42. BURNS

Parathyroid Therapy in Ulceration—Endocrine Damage from Severe Burns—Prophylactic Cortical Therapy.

A LARGE burn very soon becomes an area of ulceration, and its local treatment is essentially that of an ulcer. The same principles apply to the hastening of epithelization as underlie the healing of chronic leg ulcers (95), for instance. Parathyroid therapy certainly hastens the healing process.

PARATHYROID THERAPY IN ULCERATION—Some years ago, when the parathyroid therapy of ulceration was a novelty, an interesting case was reported, which, because of the unusual incidents related, is worth a place here. It is given as written by the Texas physician who handled the case and who, it will be noted, did a little experimenting during the treatment:

"Mrs. J. M., age thirty, weight 150 pounds, was severely burned on February 6, 1923. Two-thirds of the body was affected, some of it to the second degree, and part of it to the third degree. The first-degree burns were ignored. Improved methods of combating shock, overcoming acidosis, and maintaining the tension were carried out. After ten days of such treatment, it was noted that the patient was going to recover; and, when the mummified tissue had sloughed off and the surface was fairly free from pus, the problem was how to get the large denuded surface covered with skin. Skin grafting was out of the question because of the condition of the kidneys and the impossibility of using an anesthetic. She was given Para-Spleen Co.,* 2 sanitablets three times a day, *i.e.*, 3/10 gr. [of the active parathyroid concentrate] daily. Shortly it was noted that the skin began to grow so rapidly from the edges that it was believed that the entire area could be covered faster than by the use of skin grafts. Two physicians were called in to watch developments, and they admitted that the quickest and safest way was to continue the organotherapy. The marginal advances of the growth of skin could be clearly seen, and the skepticism of my two associates was ended by what they saw with their own eyes. We experimented by discontinuing the parathyroid and, after three days, it was clear that without the treatment there was a decided standstill in the marginal skin growth, so the sanitablets were recommenced. On April 4, the patient was discharged as cured with four small places each about the size of a half-dollar where the skin was not yet thick enough to hold the blood. Two weeks later all the ulcerated areas apparently were cured, and she was doing all her housework. She discontinued the sanitablets, however, and during the hot summer months the tension in two of these very thinly covered areas caused the skin to break down, and two ulcers were formed, each about two inches in diameter. I was not aware of what had happened, and another doctor attempted for five weeks to heal these ulcers without any result whatever. As soon as I heard of conditions, I immediately put her on parathyroid again, and in three weeks, with no other treatment than a paraffin dressing, the ulcers were entirely healed."

ENDOCRINE DAMAGE FROM SEVERE BURNS—A fatal outcome from a severe burn is now believed to be due to acute adrenal insufficiency, or the "terminal hypoadrenia" referred to in Chapter 35. A fatal burn in rabbits causes two responses: the initial stage due to shock, which is accompanied by a high blood sugar; and a secondary stage due to degenerative changes in the adrenals, accompanied by extreme exhaustion. Adrenal therapy is advisable only in the latter stage. (See the paper by H. M. Greenwald and H. Eliasberg in the *American Journal of the Medical Sciences,* May, 1926, clxxi, p. 682.)

Two definite manifestations of adrenal disorder in burns were noted by T. Nakata (*Cor.-Bl. f. schweiz. Aerzte,* Sept. 21, 1918, xlviii, p. 1283), who conducted a number of autopsies and other experimental work in connection with a study of burns. He noted that the severe toxemia accompanying bad burns causes an overstimulation of the adrenals from the first. This is followed by a depletion so serious as to be fatal in many cases. The result of the absorption of the destroyed or semidestroyed protein substances is identical with the influence of the toxins of protein putrefaction and of ptomaine and other poisons.

It has been shown experimentally that the output of adrenin is temporarily increased by burns. In his excellent and comprehensive book, "The Adrenals: Their Physiology, Pathology, and Diseases" (New York, Macmillan Co., 1929, p. 257), Max A. Goldzieher, of Brooklyn, mentions that hyperactivity of the adrenal glands not infrequently follows severe superficial burns.

It was found by L. Lattès, of Modena University (*Arch. ital. d. biol.,* 1915, lxiv, p. 123), that in animals killed within from five to seven days after a burn, the adrenal cortex shows characteristic changes—marked hyperemia accompanied by hemorrhages into the glands. These findings lend support to the view that delayed death following a burn is not so much due to primary intoxication resulting from the absorption of products originating in the burn itself, as to the secondary adrenal insufficiency that is caused by this toxemia.

Some years ago, H. G. Weiskotten, of Syracuse, New York (*Jour. Am. Med. Assn.,* Sept. 8, 1917, lxix, p. 776), gave special attention to the incidence of adrenal damage in fatal superficial burns. In addition to the usual and generally accepted findings in those who have died from severe burns, Weiskotten found that in all cases there were more or less characteristic changes in the adrenals. In fact, he considers these changes to be the most prominent and characteristic necropsy findings. The adrenals are swollen and deep red

in color. The periadrenal fat tissue shows edema. On section, certain areas suggest extensive hemorrhage obliterating the normal markings, and both the cortex and the medulla appear swollen and present reddish streaks that suggest marked congestion.

The case of a railroad fireman, 21 years old, is reported. He received extensive superficial burns of the face, forearms, thighs, and legs as a result of a boiler explosion, and died three days later. At autopsy the left adrenal weighed 20.5 Gm. and the right, 25 Gm. The average normal weight of the adrenals is 2 Gm. each.

These changes in the adrenals seem to this author to be the best kind of anatomic evidence that death from superficial burns is caused by the action upon these tissues of one or more specific toxins, originating probably in the burned area.

PROPHYLACTIC CORTICAL THERAPY—Previous clinical experience has shown that adrenalin is of value in mitigating the shock that accompanies severe burns but that it cannot benefit the adrenal exhaustion following this shock. Now that the cortical hormone is available it is suggested that it may be given to lessen the extreme adrenal insufficiency due to the expected adrenal damage. Naturally, this does not lessen the toxic influence nor change the capsular hemorrhage, but it can and does replace the missing hormone, as has been demonstrated time and again in Addison's disease (35) and in less marked degrees of adrenal insufficiency.

The suggestion is to utilize this influence in a prophylactic way in all serious burns where fatal toxemia is anticipated. Give from 1 to 5 cc. of Adreno-Cortin* intramuscularly as frequently as *every hour* for the first day or two, and later continue the treatment by giving 1 cc. every three hours.

43. CACHEXIA—LEANNESS—MALNUTRITION

Malnutrition in Children—Endocrine Influences on Nutrition—Cachexia in Malignant Disease—The Influence of Insulin—Pancreatic Digestion.

SEVERAL ENDOCRINE disorders have among their pathognomonic findings, leanness and cachexia. The control exerted upon cellular nutrition by the glands of internal secretion is such that endocrine upsets inevitably are associated with nutritional manifestations of some kind or another.

MALNUTRITION IN CHILDREN is considered to be an endocrinopathy based in some instances upon vitamin deficiency, for vitamins undoubtedly are "activators of the activators." In a consideration of the effects of the ingestion of endocrine extracts, E. M. Ellison, of Washington, D. C. (*Med. Jour. and Rec.,* May 6, 1931, cxxxiii, p. 441), states:

"Children surely need the proper stimuli from their endocrine glands to develop their vital activities. The gastro-intestinal tract may be organically perfect but is unable to perform its functions efficiently unless it receives these stimuli and those from the vegetative nervous system. This lack may be vital and the baby may die from mere failure to get the right start in life."

These defects in digestive efficiency are of tremendous import. Not only are there definite nutritional disturbances such as athrepsia and rickets (46), but reduced nutrition reduces the resistance, thus paving the way for other infections. In fact, Ellison continues (*ibid.,* May 20, p. 494):

"It is estimated by some observers that during the first two years of life approximately 50 per cent. of all children are infected with tubercle bacilli. It may be counted advisable to estimate the efficiency of the ductless glands and of the vegetative nervous system in early infancy, since they represent a part of the mechanism of defense against the development of tuberculous processes. Since it is relatively impossible to prevent tuberculosis infection of babies, the defensive mechanism must be put into good working order and kept there."

ENDOCRINE INFLUENCES ON NUTRITION—One of the outstanding symptoms of hyperthyroidism is the rapid loss in weight, due to the excessive combustion in the cells. In Addison's disease there is a serious nutritional defect probably of a nature similar to that found in tuberculosis. The endocrine regulators are overwhelmed. In diabetes also, leanness is an almost constant factor, and the French go so far as to differentiate a form of diabetes which they call *diabète maigre.* Here, of course, the difficulty is a defect in the capacity of the body to utilize cell nutriment, and the suggestion is made that, besides a pancreatic disorder of varying extent, there is a breakdown in the functions of the liver.

But there are a number of less pronounced nutritional disorders in which it is not possible to label the condition with a definite endocrine diagnosis such as those just mentioned. The purpose of this chapter is to emphasize the endocrine basis for the majority of the nutritional difficulties and all toxic disorders.

CACHEXIA IN MALIGNANT DISEASE—Whether the cachexia is connected with a serious and prospectively fatal disease as cancer, or whether apparently unrelated to any specific cause—in which case it is called malnutrition—the problems are alike in one respect at least: the malnutrition and the toxemia cannot fail to interfere with endocrine function. When a person is excessively thin and poorly nourished, it is reasonable to expect his endocrine glands also to be excessively thin and poorly nourished! Hence, the suggestion that hypocrinism is related to malnutrition.

The appreciation of the endocrine aspects of cachexia due to malignant disease has developed remarkably since the reports of W. B. Coffey and J. D. Humber, of San Francisco, regarding the alleged value of an adrenal cortex extract in the control of cancer. In many cases there have been obvious and measurable nutritional changes, some of the patients gaining considerably in weight. Whether this is due to the control of the toxemia or whether it is due to mechanical changes for the better, as in cancer of the esophagus and alimentary canal, does not appear. It is a fact, nevertheless, that Adreno-Cortin* has been used with presumed benefit in a number of cases of cachexia, although, as the reader will see in the next chapter, it is not believed that this influence is fundamental or curative.

We have already considered Addison's disease and have called attention to the therapeutic possibilities of adrenal therapy, especially of the cortical hormone. One of the heartening developments in the cases that respond to this treatment is a notable increase in weight—18 pounds in a month, for illustration. (It should be added that the patient in whom this spectacular change occurred is now dead—he died of Addison's disease, but the nutritional change and the general improvement are none the less worthy of record.)

In considering tuberculosis the nutritional factor need not be emphasized, for in all probability tuberculosis is caused by malnutrition rather than being a cause of malnutrition. From the point of view of both its endocrine and its digestive service, the pancreas is a very vital organ in malnutrition, particularly in tuberculosis. Numerous cases are reported in which pancreatin has been used as a part of the treatment with considerable benefit to the digestion, weight, and strength.

THE INFLUENCE OF INSULIN—The marked and immediate effect of insulin upon the capacity of the organism to appropriate carbohydrates has suggested the possibility of utilizing the pancreatic hormone to supplement this same capacity in other cases than those manifesting diabetes mellitus. A number of clinical workers both here and abroad have used insulin for this purpose in the treatment of certain types of persons in whom the nutrition left something to be desired.

The work that has been reported in this country is reviewed by James J. Short, of New York (*Jour. Lab. and Clin. Med.*, Jan., 1929, xiv, p. 330), who attributes the weight-increasing effect of insulin chiefly to the strong sensation of hunger that it produces. He advocates doses of about 10 units, three times a day, before meals, and suggests a diet rather high in fats since the hunger following the insulin injections in some cases may be allayed by relatively small quantities of carbohydrates.

The large German literature on this subject is reviewed by Erich Frank and A. Wagner, of Breslau, in their monograph, "Insulintherapie bei nicht-diabetischen Erkrankungen" (Leipzig, Georg Thieme, 1931). The theoretical considerations involved in this nutrition-stimulating action of insulin include a discussion of the retention of water and the influence of insulin on fat, protein, and carbohydrate metabolism. Larger doses are being used on the continent: from 40 units a day to 20 units three times a day. With such doses, of course, the carbohydrate intake must be large enough to avoid severe hypoglycemic reactions. Half an hour after each injection the patient should receive at least 1.5 or 2 Gm. of carbohydrates for every unit of insulin given; and, in case symptoms of hypoglycemia develop within two or three hours, the patient should have in readiness a chocolate bar, cake, or something with which to satisfy his hunger and relieve his symptoms.

Roy D. Metz, of Taylors, S. C. (*Jour. Am. Med. Assn.*, May 2, 1931, xcvi, p. 1456), reports that, of all the beneficial effects of insulin treatment in malnutrition, the gain in weight is of primary importance, although the general improvement frequently may surpass it. That this is brought about in the constitutionally asthenic person purely through an endocrine readjustment is as yet speculative, but it seems to be the result of the readjusted metabolism. Nevertheless, the general effects of this treatment are quite obvious. The bony irregularities are rounded out by an increase in the subcutaneous tissue. What Metz calls the "lean and hungry look" gives way to an expression that is full and pleasant. The eyes become more lustrous, and the skin acquires a healthier color and turgor. The nervous system is more stable, the mentality brighter, and the outlook on life more cheerful. The

disposition is improved. There is an increased strength and vigor. Sleep is more quiet and restful. Ambition and determination are increased. The urine is more copious and the stools are more regular. Indeed, the patient appears to have a markedly increased interest in life. These are a few of the clinical results illustrative of the possibilities of the treatment of malnutrition with insulin.

PANCREATIC DIGESTION—A phase of pancreatic service that has not received the clinical appreciation that it deserves, has to do with the relation between the duodenal hormone, secretin, and pancreatic service. It has been shown elsewhere (10) that the introduction of acid into the duodenum liberates secretin, which is the principal factor responsible for the completion of the pancreatic ferments and their liberation into the intestine. Obviously, then, secretin is a vital factor in nutrition; and we all know how common hypochlorhydria is in cachexia and malnutrition. Several suggestions have been made regarding a method of therapeutic interference in these cases: Hydrochloric acid, from 15 to 20 drops at the beginning of each meal; enteric-coated capsules of hydrochloric acid diluted with gluten; and secretin itself. The value of pancreas tail and duodenal secretin (Pan-Secretin Co.*) in diabetes mellitus (52) is due to its influence not only upon the pancreatic regulation of carbohydrate metabolism but upon the digestion and nutrition. Such an influence does not need to be limited to the treatment of patients with diabetes.

I recall an extreme case of a bedfast woman who came the nearest to being a living skeleton of any patient I have ever seen. Her weight was less than 70 pounds, but we could find no notable reason for the excessive malnutrition. She gained 40 pounds from the treatment outlined above, the most important part of which was an attempt to supplement the functions of the pancreas and the liver.

In addition to regulating such endocrine disorders as may be uncovered, it is an advantage to pay special attention to the pancreas in many types of malnutrition. Large doses of Pan-Secretin Co. (2 or even 3 tablets four times a day) plus still larger doses of pancreatin (from 15 to 30 gr. after meals) may make a great deal of difference.

44. CANCER

The Essential Endocrine Basis—Renewed Enthusiasm for Endocrine Research—The Background for Recent Developments—The Coffey-Humber Experiment with Adrenal Cortex—The Adrenals in Toxemias and Cachexia—Experience with Adreno-Cortin in Malignancy—Other Endocrine Possibilities in Cancer—Conclusion.

MEDICINE'S GREATEST unsolved puzzle has intrigued the workers along endocrine lines equally with the others. In fact, the cancer question is so obviously a matter of biochemistry that many of the most conservative and well-balanced authorities are, as never before, turning their attention to the endocrines.

THE ESSENTIAL ENDOCRINE BASIS—There are several outstanding reasons for this: (1) Cancer is essentially a disease of senescence, which is, of course, a physiological hypocrinism (65); (2) patients with malignancies commonly suffer from dyscrinism; (3) cancer is a nutritional problem, and the endocrines control nutrition; and (4) researches by the hundred have been carried out, the results of which add to the growing weight of experimental evidence that connects malignancy with the endocrines.

Despite the extent of the problem, the immense sums set aside to help in its solution, and all the accomplishments—old and new, real and fancied, clinical and experimental—the cancer puzzle is still unsolved. There is no real remedy for cancer, not even an endocrine one!

RENEWED ENTHUSIASM FOR ENDOCRINE RESEARCH—The excitement that was aroused early in 1930 throughout the United States and especially on the Pacific Coast by the newspaper reports of the treatment of cancer with an adrenal cortex extract by Walter B. Coffey and John D. Humber, of the Southern Pacific Hospital in San Francisco, has caused many physicians to ask for more information on this subject. Many are astonished to find that a large number of workers during the last thirty years or more have been studying the possible endocrine etiology of cancer and reporting encouraging results from its treatment with extracts of almost every gland. Even if, as seems likely, the Coffey-Humber treatment is proved not to be so powerful a therapeutic measure as was hoped, these men will still deserve lasting credit for showing that a potent extract of the adrenal cortex does something for the cancer patient, even in his most hopeless hour.

Before discussing this method, however, let us examine some of the information that was available before these recent developments were made.

It is interesting to note the extent of the research reported to date; the similarity between the suggestions of past decades and those of the immediate present; the broadening interest in the study of the endocrines; and the gradual change of attitude toward a subject that always has been more or less frowned at.

THE BACKGROUND FOR RECENT DEVELOPMENTS—While the work of many another investigator antedates my own consideration of the possible endocrine etiology of cancer, it will be convenient to refer here to a paper read by me at the New York Academy of Medicine, February 15, 1915 ("Organotherapy in Chronic Disease with Special Reference to Its Possibilities in Cancer," *Med. Rec.*, July 3, 1915, lxxxvii, p. 961), for, on rereading it just sixteen years later, it is very evident that the groundwork of many recent developments was foreseen then. A few excerpts follow:

"We may enumerate several promising and quite thoroughly substantiated theories [for cancer]: (1) Cancer is a chronic intoxication; (2) its incidence evidences the lack of an element in the blood which permits cell proliferation at a point of particularly lowered resistance; (3) it is essentially a disease of senescence or, as Hastings Gilford has termed it, 'cell senilism.' . . .

"We know that cellular activity is influenced by the hormones, or chemical messengers, that nutrition responds in a greater or less degree to their influence, and that it is possible to favor the reaction of the body against disease by the ingestion of certain organic extracts. . . .

"Clinically, the one essential symptom of cancer is waning cellular activity. Almost invariably, nutrition is poor and with few exceptions cancer is limited to persons past the prime of life, a fact which indicates that there may be a direct connection between the activity of those organs of internal secretion whose work ceases at this period and whose action is no longer needed. . . .

"The second of the postulates previously set forth suggests the absence from the body of a certain element, or series of elements. Just what is missing from the blood of the cancerous is not yet well known, although the work of Abderhalden and those his research has stimulated indicates that a definite series of substances may be concerned in this matter. . . .

"This missing element, to my mind, will likely be found to be produced by the endocrine system. . . . The spleen and thymus offer probably greater possibilities than many of the other glands, although I think that eventually the optimum preparation will be a pluriglandular extract containing these and other synergists."

In this paper I referred to Bayle's use of spleen therapy; Gwyer's report in 1907 that a number of cases were benefited by thymus extract; also Rohdenburg, Bullock, and Johnson's use of thyroid, thymus, and other extracts. Reference was made to the work of Seelye W. Little, of Rochester, New York, particularly to his contention that the reproduction of the reverted

cell types in cancer is caused by a relative hypofunction of certain ductless glands, and that to produce a cancerous growth such hypofunction must be primarily in an internal secretory organ derived from the same blastodermic layer as are the cells from which the cancer originates. Quoting further from this same article:

Little's "clinical findings warrant the use of several organic extracts, principally from the pituitary, parathyroids, adrenal cortex, and the islands of Langerhans. In his most recent paper, in addition to emphasizing the value of sugar feeding in many cases of cancer, he has settled down to three ductless gland extracts as essential, one each for ectodermic, mesodermic, and endodermic cancer. For the first, he uses total pituitary extract; for the second, an extract of the adrenal cortex; and for the third, an extract of the pancreas rich in the islands of Langerhans."

Ten years after the publication of this paper (1925), my associate, H. J. Achard, prepared a review of this same subject, gathering an additional weight of evidence relating the endocrines to cancer. His interesting article is entitled "The Relation of Endocrine Dysfunction to Malignancy" (*Cancer,* Jan., 1925, ii, p. 118). It is principally to this paper and to Paul Luttinger's article, "Endocrines and Cancer (Review of Recent Experiments)," published in the same issue of *Cancer,* that I am indebted for many of the earlier citations immediately following:

The Adrenals—In the first edition of his work, "Internal Secretions and Principles of Medicine" (Philadelphia, F. A. Davis Company, Vol. I, 1903), Sajous expresses the opinion that certain growths, particularly the more malignant forms, sarcoma and carcinoma, seem closely connected with adrenal insufficiency and its normal consequences. He says further:

"We have seen that trypsin, fibrinogen, and the oxidizing substance were simultaneously necessary to insure the destruction of cells even in vitro, and, furthermore, that this process regulates, in addition, the presence of alkaline salts. That the destruction of worn-out or degenerated cells is a function of these very elements in the blood is evident. Insufficiency of the adrenals, therefore, by reducing the relative proportion of these four constituents in the blood stream must correspondingly inhibit this physiological process in all parts of the organism." (*Ibid.,* p. 785.)

Mahn (1904) treats cancer of the upper respiratory tract with 10 per cent. adrenalin solution, with improvement but no cure. These results are confirmed by Ichard (1904). Revello (1905) reports an ulcerated carcinoma of the lip cured by painting it with adrenalin solution. Sajous (1908) expresses the opinion that the functions of the adrenals not only explain the pathogenesis of cancer but suggest the class of agents that will master the disease (*loc. cit.*). Reicher (1910), experimenting with sarcomatous rats, cures 98 per cent. of them by paratumoral injections of adrenalin in physiological salt solutions. Echtermeyer (1911) reports great improvement in carcinoma of the base of the tongue with adrenalin injections. Engel (1912) obtains good results with

the synthetic and natural adrenalin. Pinkuss (1912), on the contrary, observes no beneficial effect in cancer of the breast treated with adrenalin. Centanni (1912, 1914), who introduced experimentation in vitro and was the first to use capillary tubes for the analysis of the chemical products of cell growth, shows that adrenalin has a stronger power of influencing the growth of cancer cells in vitro than any other substance. The clinical findings of Little (1914) warrant his use of adrenal cortex, as well as pituitary and pancreas, in the treatment of cancer. Schoull (1928) reports spectacular results with Naamé's treatment in cancer—injections of adrenal, mammary, and thyroid extracts.

The Liver—Macdonald (1923) attempts to control internal cancer with liver extracts, and his failure turns out to be a success, for he uncovers the possibilities of hepatic depressor therapy (13). Howitt (1926) injects extracts of embryo pig liver into cancerous mice. The results are so encouraging that liver extracts from beef are tried on hopeless, inoperable cases of human cancer. Results are decidedly encouraging. The next year he reports unusually good results from liver extracts in the treatment of inoperable cancer. In one patient there was a complete disappearance of the tumor mass and in others, still under treatment, a reduction in the size of the growth.

The Mammæ—Deelman (1923) believes that the function of the mammary gland favors the occurrence of cancer of the breast in its functional period, while it exerts an inhibitory influence later on. Peller remarks that the study of mammary carcinoma, in a large number of patients affected with cancer of the genital organs, shows that pregnancy exerts a protective effect. The irritation, which is an indubitable factor in genital carcinoma, is far less evident in mammary carcinoma. Naamé (1928) uses mammary extract in cancer of the breast because the menses are usually abundant in these patients. Berman (1931) treats eighteen cases of bleeding nodular uterus with daily injections of mammary extract. Relief of bleeding and a decrease in the size of the uterus follow the regular injection of mammary extract.

The Ovary—Beatson (1897, 1901, 1905) attempts to cure inoperable carcinoma of the breast by castration. Bilateral ovariectomy is practised by Fichera (1909). Leo Loeb (1916), seeking to ascertain the influence of corpus luteum on the development of mammary carcinoma in mice, finds that removal of the ovaries not only arrests growth of the mammæ but also inhibits development of the tumor. He also finds (1923) that common carcinoma of the mammary gland is referable to either an hereditary factor or an internal secretion of the ovary. Dœderlein (1923) cites as a predisposing factor to the so-called precancerous condition, disturbances of the endocrine glands, notably the ovaries and the thyroid. Little and Murray (1929) conduct experiments on mice which demonstrate that some ovarian secretion is one of the causative factors in the formation of cancer of the breast. Berman (1931) uses corpus luteum in the treatment of twelve cases of painful breasts with nodules. All responded with a lessening, then with a cessation of the pain and a decrease in the size of the nodules to the point of being barely palpable or disappearing entirely.

The Testes—Graf (1909) and Amalgia (1912) show that ablation of the testicles prevents transplants from taking. Woglom (1911) finds that tumors develop more rapidly and reach a larger volume when transplanted into the testicle. José Carra (1924) observes that the testicle cells stimulate growth of neoplastic cells. Apolant, Fichera, and Theilhaber find that gonad extracts inhibit the growth of tumors in experiment animals. In Elaner's experiments (1926) growth of inoculated tumors seems to be inhibited by injections of testicular extract. Jacqmin (1929) concludes from experiments on mice that castration before or after puberty appears to increase the malignancy of tar tumors and to hasten the appearance of metastases. Castration before puberty has an opposite effect on the receptivity for tar cancer and the receptivity for inoculation cancer.

The Pancreas—Little (1914) believes that his clinical findings warrant the use of several organic extracts, principally from the parathyroids, pituitary, adrenal cortex, and the islands of Langerhans. Shaw-Mackenzie (1923) shows that tissue lipolysis is defective in cancer. He believes that insulin is one of the antilipemic, prolipolytic substances that should be used in the treatment of cancer. Fenwick (1925) says, "I am treating every cancer patient with injections of insulin, in addition to radium or deep therapy, and many of these ask for the injections to be repeated." Weiss (1926) implicates the pancreas in the causation of cancer, referring to its common senile involution and the frequent concurrence of diabetes. Silberstein (1925) produces cancer in mice and then treats them with insulin. In the majority of cases the growth is arrested or disappears entirely. Silberstein, Freud, and Revesz (1927) conclude from extensive experiments that the treatment of cancer with insulin may cause the disease to come to a standstill, and even in inoperable cases may cause a retrogression whereby the tumor may become amenable to operation. May (1927) obtains relief of pain and other beneficial effects in cancer patients by the use of liquid preparations from fresh pancreas glands administered orally and subcutaneously. He also uses a dried extract given in capsules, and advises the use of half a pound of fresh gland (boiled about fifteen minutes) every day. Coffey and Humber (1930) state that observations cause them to believe that where the blood-sugar level is high the patient does not react so well to their extract, and that sloughs are much slower in forming unless the patients are put on a low carbohydrate diet.

The Parathyroids—Behan (1929) emphasizes the importance of the relief of pain in cancer. He obtains excellent results from the use of alkalies intravenously and orally, calcium by intravenous injection, and parathyroid by mouth and intramuscularly, in addition to other measures. Folkmar (1930) reports good results from the adjuvant use of parathyroid and spleen in a number of her cancer patients in whom the ionized calcium content of the blood was 30 per cent. or more below normal. Reding and Slosse (1930) find that alkalosis always exists in cancer, and that they can reduce it with parathyroid therapy. Thompson (1931) separates the blood-calcium-raising factor of the parathyroids from a growth-inhibiting factor, and finds it of value in carcinoma and sarcoma.

The Pituitary—Norgate (1922) uses pituitrin in thirty-six cases of inoperable cancer. It is followed by a delay in the onset of the secondary gland troubles and a tendency toward abortion of the growth; no secondary deposits are observed in other parts of the body. It is especially considered as a means of controlling hemorrhage; it delays growth by cutting off the blood supply and prolongs life; also benefits cachexia. Seel (1924) produces tar tumor in rabbits. The onset of the tumor is distinctly retarded in animals that are injected once a week with a posterior lobe extract, and the proportion of malignant tumors is less.

The Spleen—In 15,000 autopsies, Williams (1908) finds only two spontaneous tumors. There is no reference to malignant tumors in the comprehensive statistics of Kolb and Buday (1910). Brancati (1911) and Cimoroni (1912) cannot successfully transplant malignant growths into the spleen. Braunstein (1911) finds that animals deprived of their spleen become more susceptible to cancer. Oser and Pribram (1913), Braunstein (1911), and Apolant (1913), all of whom have observed enlargement of the spleen in tumor-bearing animals and the increased susceptibility of splenectomized animals, find that the administration of splenic substance prevents the transplants from taking. Lewin and Meidner (1912) observe that spleen substance increases the refractory period. José Carra (1924), in his experiments in vitro on the transplantable adenocarcinoma of the mouse in contact with the spleen, testicle, adrenal capsules, liver, and kidney, notices that the spleen exercises a constant and clearly marked inhibitory action on tumor cells. Naamé (1928) claims the successful use of a splenothymic extract in sarcoma.

The Thymus—The first to use thymus extract in the treatment of carcinoma is Foulerton (1902, 1904). Thymus extract or direct injection of the gland, emulsified in glycerin, into the body of the tumor, has an inhibitory action on malignant growths. Kaminer and Freund, whose work began in 1911, show that the destructive power of blood-serum upon cancer is greatest in childhood and least in senility. They think it might be connected with the evolution and involution of the thymus. Rohdenburg, Bullock, and Johnson (1914) recommend thymus, thyroid, and other extracts as part of the treatment of cancer. Boulogne (1924), after experimental work with rabbits, administers thymus extract to advanced cases of cancer with satisfactory results. Babes (1930) finds that experiment animals affected with tar cancer show atrophy of the thymus. This was considerably more marked in those that did not show cancer. Hanson (1930) reports encouraging experimental and clinical work with a thymus extract.

The Thyroid—At the Fourteenth International Congress of Medicine, Lorand (1903) reports having found atrophy of the thyroid in all cases of malignant growths, and suggests that thyroid extract be administered as a routine measure to all cancer patients. Foulerton (1904) uses fresh extracts of thymus and thyroid glands for cachexia. Rohdenburg, Bullock, and Johnson (1911) remove various organs such as the thyroid, testicles, and spleen from susceptible animals with contradictory results, though they find that thyroid therapy has an inhibitory effect in contrast with the results from

thyroidectomy. Beveridge (1915) believes that the theory of perverted metabolism as a cause of cancer is more plausible than other theories; he believes that the endocrines play their part in metabolism and that the thyroid probably is the most important, while the pancreas and pituitary also must be reckoned with. Round (1918) suggests a relation between carcinoma and hypothyroidism, and advises prophylactic measures against goitre. Bayard (1919) points out a relation between carcinoma and hypothyroidism, and by means of goitre prophylaxis hopes to control cancer. Little (1922) seeks to establish the important part played by Graves' disease, Addison's disease, and diabetes in cancer. He claims that each of these diseases presents many characteristics common to cancer. Dœderlein (1923) cites, as a predisposing factor to the precancerous condition, disturbance of the endocrine organs, notably the ovaries and the thyroid. Engel (1924) states that the hormone theory of cancer has been demonstrated experimentally and that differences exist between the hormones, the thyroid and the thymus inhibiting carcinoma while the pituitary accelerates its growth. José Carra (1924), who conducted experiments in vitro, demonstrates that the thyroid has a stimulating effect on growth of neoplastic cells. A relationship between cancer and endemic goitre is postulated by Stiner (1924), who refers to the assertion that cancer was more prevalent in Switzerland than elsewhere. Naamé (1928) systematically prescribes thyroid to antagonize the cellular anarchy and to combat the local hypocytopoiesis by an organotherapeutic medicament varying with the site of the cancer, the sex of the patient, etc.

THE COFFEY-HUMBER EXPERIMENT WITH ADRENAL CORTEX—The foregoing review, which does not pretend to include a reference to all who have studied the endocrines in relation to cancer, brings us down to the work of Coffey and Humber. Their first announcements in the early months of 1930 surprised the medical profession in America and set the pulses of many a sufferer from cancer athrilling with the hope that at last a real advance had been made in the treatment of their own hopeless disease.

In January, 1930, it was reported in the press that an extract of the adrenal cortex of sheep was being used successfully in two San Francisco hospitals—the Southern Pacific Hospital and the St. Francis Hospital. A news item like this was "a scoop," and doubly so when the sponsor of the new remedy was no less than the Medical Department of the great Southern Pacific Railroad and the originators were the Medical Superintendent and his associate. Naturally the press "played up" the news.

On February 17, 1930, I heard these gentlemen outline their accomplishments and their hopes, and, judging from what was said and from what I have read of their experiences, they have worked alone, their ideas were original with them, and their reports, as they say, "have been suppressed" voluntarily for years.

According to Coffey, he came to be interested in the internal secretions by his studies of the sympathetic nervous system. Finding the information on that subject quite limited in current literature, he and Humber were forced to do some original work on the anatomy of the sympathetic nervous system. This led them eventually to a consideration of the endocrines, for the sympathetic nerves were consistently traced back to the internal secretory glands. It was shown how intimate is the control of these glands by the sympathetic, and that, in the case of the adrenals at least, it is their sole innervation.

It is well known that the adrenal medullary principle is a pressor substance of marked activity; and, since these workers were looking for a means of controlling hypertension, they naturally looked to the adrenals to supply the balancer or, as they called it, "the stabilizer." They insisted that they had found this stabilizer in the cortex, and this formed the basis for their work in developing their adrenal cortex extract.

Many extracts were made by them and used in an attempt to lower the blood-pressure and to control tissue growth. During the previous five years, they had used first thyroid, then extracts from the thymus and the adrenal cortex, and also pluriglandular combinations. At present they are using what Humber calls "a special single extract from the adrenal cortex." Their claim is:

"We are positive that we have an active principle of the adrenal cortex which causes no local or systemic reaction, but which in twenty-four hours brings about remarkable control of the pain in cancer and within a week, a softening of the tumor, and later, sloughing. . . . Our extract undoubtedly has caused this necrosis or liquefaction, and we cannot explain the alleviation of pain that occurs in a few days from the beginning of treatment, but in this alone we feel that we have accomplished something worth while."

It is interesting to note that the direct clinical contact between the endocrines and cancer was made while these workers were attempting to find a means of stabilizing the blood-pressure in a hypertensive patient who also had a carcinoma of the bladder (*California and West. Med.*, Sept., 1930, xxxiii, p. 640). In the most recent paper by these authors they state that, in the six months preceding, 2600 patients came under their observation. Many of these have improved and returned home, while 13½ per cent. have died. They believe that patients who have had X-ray or radium show a tardiness to react to treatment.

THE ADRENALS IN TOXEMIAS AND CACHEXIA—In the light of more recent developments in the study of cancer, it almost fills one with awe to turn back to the writings of Sajous and read there the clear, detailed suggestions regarding the cause and the treatment of this disease. The following items

are taken from the 1908 edition of his "Internal Secretions and Principles of Medicine" (Philadelphia, F. A. Davis Company, pp. 1397, 1413):

"Advanced age is the predominating predisposing cause of cancer, but since the disease does not occur in all aged individuals, an additional predisposing factor is necessary. This factor may be said to include all morbid influences, inherited or acquired, which tend further to debilitate the organism. Although cancer is witnessed among the poor and ill-fed, and its development may follow exhausting toil, great anxiety, prolonged illness, and other debilitating conditions, it occurs at least as frequently among subjects who have not been exposed to similar untoward influences, *i.e.*, the well-to-do and well-fed, and even the overfed. In all these, however, inherited vulnerability to disease, which means inadequate activity of the autoprotective mechanism—the adrenal system—may none the less be present, and when advanced age is reached, the organism is unusually vulnerable to disease among the rich and poor alike."

"The function of the adrenal system not only explains the pathogenesis of cancer, but it also points to the class of agents which will master this dread disease."

The reader who has followed this subject before (35) realizes that the idea of endocrine depletion as an ordinary experience, as well as the idea of endocrine rehabilitation or support as an equally ordinary measure, was comparatively new twenty years ago. But since that time many things have happened, one of them a terrible epidemic of influenza (1918) in which tens of thousands died and hundreds of thousands were "flattened out" by the unusually terrific toxemia (69). This experience has made many a physician "adrenal minded."

From that time to this, I have hammered on the adrenal cause of this depletion and the reasonableness of adrenal support in the postinfluenzal let-down as well as in all toxic depletions (35).

But what has this to do with cancer? Just this: The outstanding endocrine symptom of cancer is *hypoadrenia*. Cachexia is essentially an adrenal picture (43). The toxemia of malignant disease cannot but affect the endocrine glands, as does every poison that circulates in the blood and, therefore, passes through every ductless gland. This was the reason for my position *in 1915*, and for my unusual interest in the Coffey-Humber experiment.

True, the attempt to support the adrenals in the played-out, toxic cancer case does not effect a cure of the malignant growth. This therapy, however, has been applied with benefit times without number, and it is none the less rational although its results are inevitably limited.

Adrenal support is beneficial in overcoming at least some of the aspects of cachexia. Excessive weakness in many patients with malignancy has been

symptomatically improved, but we have never felt that anything approaching a cure was in sight, although it is evident that the San Francisco workers have had this idea.

EXPERIENCE WITH ADRENO-CORTIN IN MALIGNANCY—Since the autumn of 1929, when Adreno-Cortin* was finally stabilized and freed from epinephrine (9), it has been used more and more in patients suffering from malignancy. I can state here in a very short sentence the conclusions based on the experiences of hundreds of physicians with thousands of patients over a period of more than two years: *Adreno-Cortin is not a remedy for cancer, but it is a most helpful measure in the cachexia of cancer patients.* I fear that the same is true of the Coffey-Humber product.

The reports to date stress subjective, temporary improvement of symptoms rather than of the disease itself. The strength seems to be increased, the pain is lessened, and there may be a gain in weight. Some of these patients are supposed to have been *cured,* but it is submitted that others with undoubted ultimate malignant disease have appeared to have been *cured* following other treatment or no treatment at all!

OTHER ENDOCRINE POSSIBILITIES IN CANCER—I would not have the reader conclude from the foregoing recital that adrenal cortex is the only endocrine product with inherent potentialities for the solution of the cancer problem—it is but one, for there is increasing evidence that some of the other endocrines are also important. A few points from the recent literature *may* hold the winning number—one never knows.

One of the workers in King's College, London, J. H. Thompson (*Brit. Med. Jour.,* May 9, 1931, i, p. 819), has succeeded in separating the blood-calcium-raising factor of the parathyroids from a growth-inhibiting factor:

"Extracts of parathyroid glands thus prepared have been injected intramuscularly into human subjects suffering from various types of carcinomata and sarcomata, including spheroidal-celled carcinoma, columnar-celled carcinoma, endothelioma, sarcoma, and glioma. The cases have been treated at the Soho Hospital for Women, the Westminster Hospital, and St. Bartholomew's Hospital. Some improvement has been noted, and the results are sufficiently encouraging to warrant a continuation of the investigation."

In *Minnesota Medicine* (Jan., 1930, xiii, p. 17; also Feb., 1930, p. 65), Adolph M. Hanson, of Faribault, Minnesota, reports some interesting experimental and clinical findings from the use of an extract of the thymus gland. Hanson's work is of special interest in view of the fact that during 1922 and 1923 he was the first to produce a physiologically standardized parathyroid extract, antedating Collip by a considerable margin. This

work with thymus was based on the theory that epithelial tumors result from the loss of the natural cellular influence that maintains the normal mitosis or cell division. Hanson says:

"With the idea that the internal secretion of the true thymus is locked up in the giant epithelial cells, and on the supposition that this thymic internal secretion preserves normal epithelial health throughout the entire body, *i.e.*, that it controls and keeps up normal epithelial growth and cell repair, I set myself the task of isolating the true thymic hormone. In order to do this it seemed that a method of extraction that would break down the gland completely and that would exclude the lymphoid elements held out the best hope of solution."

This preparation, known as "karkinolysin" (because it appears to exert a lytic effect upon certain malignancies), seems to have a more definite and selective action in the epithelial types of cancer, that is, in carcinoma. It is given by daily intramuscular injections for several months, and there follows a series of results that appear to be very interesting.

CONCLUSION—Granting that organotherapy has most obvious limitations as a remedial agency in cancer, shall we deny our patients such limited good as it can now offer them? Admitting that the avowed hopes of some of the workers in this field have not been realized to the satisfaction of authority, shall we pass our judgment and occupy ourselves with something else? The answer is, of course, NO!

There can be no question that the endocrines have given us remedies literally amazing in their possibilities. Remember the revolution in our conception of myxedema, cretinism, etc., when Murray announced the beginnings of thyroid therapy (1889); the changed outlook on asthma, shock, etc., when adrenalin was offered by Takamine and Aldrich (1901); the wonders of the posterior pituitary principle in labor, first told by Blair Bell (1909); the miracles of Banting's insulin (1922); *and some others*. "The end is not yet," and surely the riddle of cancer is not forever to remain insoluble to a profession responsible for such advances as, within a comparatively brief period, have been unfolded before their astonished eyes in so many other phases of medicine. I firmly believe that, when the time comes for us to look back at the fruitless years in which we attempted to solve this great problem, we shall find that those who "were playing with the endocrines" came nearest to its solution.

45. CARDIOVASCULAR DISEASE

Angina Pectoris — Hypertension — Hyposphyxia — Neurocirculatory Asthenia — Hypotension — Myocardial Disease — Syncope and Shock — Tachycardia.

SINCE ENDOCRINE function regulates detoxication and is closely related to the function of the sympathetic system, it is easy to see that prolonged dyscrinism may predispose to cardiovascular imbalance and even degeneration. But the cardiac and circulatory aspects of endocrinopathic cases are not usually primary and functional, hence they do not respond very well to endocrine treatment. Yet, in recent years, a number of things have happened that open up some interesting possibilities in the supplementary treatment of several of the more functional cardiovascular disorders, notably the tachycardia of hyperthyroidism, the hypertension of hypohepatism, and the simpler types of myocardial degeneration.

ANGINA PECTORIS—Coronary sclerosis and other forms of arteriorenal sclerosis undoubtedly occur in maximal endocrine disorders. The defective cellular chemistry of hypothyroidism certainly affects the heart structures; the hepatic detoxicative breakdowns that cause hypertension also lay the foundations of the intimal changes that eventually lead to arteriosclerosis; and the stress of the cardiovascular instability of hyperthyroidism leaves its mark upon the heart muscle itself. There are other factors of similar character that play their parts also, but the three enumerated here are responsible for many an ultimate cardiovascular syndrome. Unfortunately, these coronary changes are too subtle and they develop upon etiologic foundations of such an insignificant and unheralded nature, that usually there is not much therapeutic encouragement to be obtained from a knowledge of these facts.

Some recent developments in organotherapy offer symptomatic help in early cases of angina. As these new remedies—the heart hormone (12) and the circulatory hormone from the pancreas (15)—are used chiefly in hypertension and myocarditis, it will be convenient to consider them under these headings.

Dyscrinism stresses the heart directly and indirectly, and no matter what the name or stage of the cardiovascular disorder, if there are some associated endocrine disorders, every form of indicated treatment will be more effective as it is possible to overcome these endocrine factors. Perhaps more can be done by and through the liver; and, besides the encouragement of hepatic detoxication, it is always helpful to "wring out the liver" (104).

HYPERTENSION—The arterial tension depends upon the beat of the heart, the elasticity of the vessels, and the amount and viscosity of the blood. These physical factors are subject to the control of the vasodilator and the vasoconstrictor system of nerves, which, in its turn, is controlled to a large extent by influences originating in the endocrine glands, chiefly the adrenals.

High blood-pressure is a dual clinical entity—a functional disorder or an organic one. Our concern here is with functional hypertension, known also as essential hypertension and sometimes as hyperpiesis.

There are two phases of the treatment of hypertension to be discussed here: (1) the control of the endocrine features underlying the increased pressure, and (2) the control of the pressure itself. The former involves three types of endocrine hypertension: (a) adrenal, (b) hepatic, and (c) thyroid, each of which will be considered separately. The control of the increased pressure is another matter—it happens that certain endocrine measures actually may reduce the blood-pressure, as may be done by recourse to certain drugs, *e.g.*, the nitrites. It is desirable, however, to make a definite distinction between the treatment of the endocrine causes of hypertension and the endocrine treatment of the hypertension itself; for, while both measures are desirable and rational, there is a great difference between them. It is one thing to control a fundamental cause and thereby remove its effect, and another to overrule the effect, thus leaving the cause to reassert itself when the control over it is removed.

Herein lies the complexity and difficulty of this matter. The problem of hypertension involves far more than the discovery of the increased tension and its immediate reduction, as will now be explained.

Adrenal Hypertension—Hyperadrenia can cause high blood-pressure, but most often hyperadrenia is an ephemeral condition due to or associated with sympathicotonia. Its treatment consists in the control of the adrenal irritating features—toxic, emotional, or infective.

There is, however, a form of adrenalism in which a combination of circumstances "keeps the adrenal pressor mechanism on edge." This is rare, for nearly always the overstimulation will deplete the adrenals, thus causing a hypotension rather than a hypertension, as we shall see. Nevertheless, in Chapter 35 attention is called to the recent work of G. W. Crile, of Cleveland, with adrenal sympathectomy and to Galatà's work with unilateral adrenalectomy for the control of this rare type of adrenal hypertension.

Hepatic Hypertension—Defective hepatic detoxication can and does cause a functional increase in the blood-pressure. The liver is supposed to destroy

certain pressor wastes, notably guanidine and bodies akin to it. Quoting from my book, "Practical Hormone Therapy" (London, Baillière, Tindall & Cox, 1914, p. 159):

"Arnold Lorand believes—and his opinions are corroborated by A. Gilbert, H. Strauss, and others—that the liver is a gland with an internal secretion that is strongly antagonistic to intestinal poisons, destroying toxic products brought to it from the intestine by the portal vein. This antitoxic power claimed for the liver is dependent, not upon the blood that may be present in the organ, but upon the liver tissue itself; and the activity of this organ in destroying toxins must be due to some chemical substance at present unknown. A part, at least, of this power remains in vacuum-dried extracts, and is probably the source of the benefits that follow its therapeutic administration."

This "chemical substance at present unknown" (in 1914) apparently is the hepatic detoxicative hormone; and, as the reader has already seen (13), this hormone is believed to act by catalysis upon the capacity of the liver to destroy these waste products, rather than by producing circulatory changes such as we expect from the nitrites. It is true, however, that the hepatic detoxicative hormone, because of its effect upon the liver physiology, does indeed cause an increase in the circulation in the liver as a prelude to the increased cellular activity, which in a mechanical way may reduce the blood-pressure because of the great blood capacity of this organ.

Thyroid Hypertension—The frequency with which excessive arterial tension is associated with poor cellular chemistry has prompted many to connect it directly with hypothyroidism, the chief cause of metabolic insufficiency. These workers do not all blame the thyroid specifically for high blood-pressure, but they assume that its irregularities contribute to a general state which eventually is the cause of either functional or anatomical changes that help to establish this condition.

More than thirty years ago Eugene Hertoghe, of Antwerp (*Bull. Acad. roy. de méd. de Belgique,* 1899, xiii, p. 231), called attention to the changes wrought upon the rate and tension of the pulse by the disturbed metabolism of thyroid insufficiency, as well as by its antithesis, thyrotoxicosis. I fully agree with Hertoghe that the thyroid never can be functionally inefficient without a resultant toxemia of varying degree due to lessened activity in the cells themselves. E. Slosse, the Brussels physiologist (*Bull. Acad. roy. de méd. de Belgique,* 1913, xxvii, p. 697), insists that the thyroid hormones (he uses the plural and refers to two or more thyroid products) exert a deaminizing influence. He believes that a part of the oxidation of certain waste products is dependent upon the endocrines, particularly the thyroid and the liver.

It is well known that high blood-pressure frequently occurs in obese persons. It seems clear that these individuals are not oxidizing with sufficient rapidity the products of destructive metabolism. Therefore, because of the deficient stimuli from the thyroid and associated glands, certain protein wastes accumulate which overburden the emunctories and thereby directly raise the arterial tension, not merely from the cause just mentioned, but from the irritating effect of these products upon the adrenal pressor mechanism.

Any consideration of the relation between endocrine obesity and hypertension necessarily reminds us that this type of obesity is more common in women, especially at the menopause. Hypothyroidism also is more frequent at this time, and it is quite certain that the dyscrinism of this particular period of a woman's life predisposes to increased arterial tension. In his book, "Middle Age and Old Age" (London, Oxford University Press, 1925), Leonard Williams, of London, calls attention to the fact that the blood-pressure frequently is found to be somewhat increased before each menstrual period. This probably is due to the fact that an increased pressure is actually necessary to produce the flow. As an illustration, Williams cites the case described by Francis Hare, in which the use of amyl nitrite caused a cessation of the menstrual flow by lowering the blood-pressure. He also states that ovarian substance acts as a vasodilator, and that its chief effect is on the pelvic vessels, though it also has some effect on the circulation in other parts of the body. As a temporary menstrual vasodilatation is accomplished by the harmonious action of the thyroid and the ovaries, there must always be a corresponding vasoconstriction in the rest of the body. It is this fact that is believed to be responsible for the elevated blood-pressure at the normal period. The hypothyroidism that is so common at or near the menopause adds another factor to those already mentioned which bring about an increase in the blood-pressure.

Now let us consider the possible relationship between Hertoghe's thyroid infiltration and arteriolar hypertension from the standpoint of physics. For example, a given cell, which may be located almost anywhere in the body, is not able to maintain its normal chemical activities. As a result, the cellular activities are lessened still further because the semioxidized wastes of that cell are allowed to accumulate. Since these substances are not properly prepared for elimination, they remain behind and, as a result, there is a swelling of the cell according to the law of physics that maintains the osmotic tension. In other words, this increased osmotic tension in the cell draws fluids from elsewhere to keep its tension balanced with that of the fluids around it, thereby infiltrating, or dilating, or swelling, or water-logging the cell.

This occurs in all parts of the body, including the farthest ends of the circulatory system. May it not be that the infiltrated cells that surround these microscopic vessels are mechanically interfering with the flow of blood, thereby reducing the circulation in a comparatively large area with a corresponding increase of effort on the part of the heart muscle to force the blood through these finest capillary meshes?

Many clinicians express the belief stated years ago by L. F. Barker, of Baltimore (*Ohio State Med. Jour.*, Oct., 1920, xvi, p. 709), that high blood-pressure may depend upon a narrowing of the lumina of the arterioles in the precapillary areas. Thus there is a very real mechanical cause for hypertension, and that it may be essentially thyroid in origin is confirmed by the therapeutic test. Many patients have found that a course of thyroid therapy has a decidedly beneficial influence upon various manifestations of the toxemia. It has been noted also that an associated high blood-pressure due to the mechanical obstruction of the circulation in the ends of the circulatory structures, is reduced following the increase in cellular chemistry resulting from the thyroid stimulation of metabolism. Thyroid therapy, then, reduces this type of blood-pressure in two distinct ways: It stirs up the cellular chemistry, thus reducing the toxemia, and at the same time it brings about a mechanical removal of circulatory interference.

The tendency to cold hands and feet commonly found in hypothyroidism is, I believe, due to exactly the same cause as the increased blood-pressure, namely, the cellular infiltration already mentioned. This cellular infiltration also involves the larger glandular structures, particularly the liver. It is reasonable to suppose, therefore, that with thyroid insufficiency one would find infiltration of the liver itself and hepatic circulatory stasis. With this is found the very common syndrome of hepatic insufficiency, namely, cellular toxemia and its numerous results, including endocrine hypertension. Thus the two common causes of this condition are often linked together.

A Routine Treatment—Naturally, a patient does not come labeled with the particular kind of hypertension from which he is suffering, and a wrong diagnosis predicates failure from the best of treatment.

High blood-pressure, due to nephrosclerosis and arteriosclerosis, obviously is a compensatory and necessary development. Attention to hepatic detoxication certainly cannot change the permeability of the kidney nor the pliability of the arteries. When the report of the renal function test (phenolsulphonephthalein) is below 40 per cent., the prospects are that the hypertension is organic in nature, and that an attempt to reduce it from this functional standpoint will not be successful.

Again, hypertension due to hypothyroidism, just referred to, is not likely to be satisfactorily modified by hepatic detoxication. This may help, for, as we have seen, the toxemia in hypothyroidism nearly always puts additional stress on the liver, and encouragement of the liver function is of general value. Nevertheless, hypothyroidism cannot be treated satisfactorily in any other way than by thyroid therapy; the response to this gives both clinical benefit and diagnostic conviction.

The rest of the cases of high blood-pressure, perhaps 40 per cent., may be spectacularly influenced by Anabolin.* With the reduction in the blood-pressure following the first few injections, there comes an improvement in the patient's well-being which convinces him that something more is being done for him than the reduction of the hypertension itself. In fact, the euphoria is often the most noticeable development following the use of this hepatic hormone. Treatment routinely is carried out thus:

Having carefully studied the patient, estimating the urinary elimination and making a series of blood-pressure records, proceed with the usual preliminary hygienic and eliminative measures. Accomplish as much as possible by general methods. Then, after taking a blood-pressure record, inject ½ cc. of Anabolin Solution intramuscularly. Have the patient rest from one-half to one hour, then take another blood-pressure reading and record it. If the pressure remains unchanged, or has fallen only slightly, the patient may go home. The blood-pressure is read again on the next day. If it has fallen from 10 to 30 points, another injection of 1 cc. is given, followed by a rest period, and another blood-pressure record is made. If, however, the tension has fallen 50 points or more (and this is not infrequent), postpone the second injection until the next day. If, after the second dose, the tension remains at its previous level or is reduced but slightly, the procedure is simple: Give 1 cc. daily for five days, then every other day for two weeks longer.

Whether the patient has reacted markedly to the injection with a reduction of 100 points (in cases where the blood-pressure originally was 250 mm. or more), or whether the blood-pressure change has been negligible, the dosage may be modified as indicated. In any event, the preliminary care in the administration of the first few injections will avoid any discomfort due to the inadvertent use of Anabolin where contraindicated. (Should any signs of anuria appear, the best thing to do is merely to discontinue the injections and give a diuretic—water usually suffices.)

It is neither necessary nor advisable to give more than 2 cc. of Anabolin Solution daily; nor is it advantageous to continue the injections for more than two or three weeks in any one series. In the majority of suitable cases, a

preliminary series of injections, such as has been suggested, will suffice. The benefit, which will have been decided in this comparatively short period, may be prolonged and in many cases made permanent by continuing the remedy in tablet form—1 tablet from one to three times a day, depending on the subjective findings and, of course, the blood-pressure figures. In many cases Anabolin tablets have been given alone, *i.e.,* with no previous injections, with almost as beneficial results as with the hypodermic method. Here the suggested dosage is 1 tablet the first day, 2 the second day, and 3 a day (usually at or near meals) for several weeks or months thereafter.

A warning should be given about promising results. The benefit from hepatic detoxicative catalysis depends entirely upon the responsiveness of the liver, which is always an indefinite matter. It should be said further that the majority of these patients have acquired a certain physiological habitus due to their mode of living—diet, elimination, etc.—and in many cases there will be a gradual return to the previous status.

Hypohepatism (66), a functional hepatic breakdown due to physiological strain, is an indication for hepatic support just as hypoadrenia is an indication for adrenal support. For many years the French have believed that liver extract (an ordinary desiccation of the hepatic parenchyma) is a remedy with real potentialities in *l'insuffisance hépatique.* A preparation combining hepatic extract with desiccated spleen, known as Hepato-Splenic Co.,* was used in this type of disorder for more than ten years. The perfection of Anabolin obsoleted this formula, so in 1927 Anabolin (gr. ¼) was added to it, and boldine hydrochloride (gr. 1/60) also was included because of its influence on hepatic activity. These additions augment the secretion of bile and increase the elimination of urea.

The principal use of this formula has been to supplement Anabolin in suitable cases and to prolong its influence. Many physicians, having obtained some satisfactory results in the treatment of hypertension in this way, on discovering that the patient had reverted to his former condition and discomfort, have asked why the benefit was not permanent. The answer is that nothing can change the habits of a lifetime, and unfortunately circumstances will cause the return of the hepatic detoxicative depletion unless some special effort is made to avoid it. Hepato-Splenic Co. has been developed especially to maintain the hepatic detoxicative service or to nudge the liver. From 3 to 6 tablets a day are given for months after Anabolin has demonstrated its efficacy and the essentially hepatic nature of the difficulty.

Organic Hypertension—Until recently we have not had much faith in the possibility of effectively interfering in the organic cases of angina, arterio-

sclerosis, and hypertension of an anatomical nature. It is claimed that the new muscle hormone (12) and the new pancreatic circulatory hormone (15) are actually capable of bringing about benefit in this type of hypertension. The reports are becoming more numerous, but the outcome is still undecided. Many of the patients treated so far were apparently mixed types, partly functional and partly organic. It may be that the alleged benefit affected a phase of the syndrome that might have responded to other treatment.

Suffice it to say that the present accepted list of endocrine principles is bound to be extended. We have not come to the end of all knowledge on this subject. Who knows that Panocrin* (15) may not broaden our control of the organic type of hypertension, and that Lacarnol (12) may not lead to a new conception of sclerotic anginal disorders?

HYPOSPHYXIA—A. Martinet, of Paris (*Presse méd.*, 1913, xxi, pp. 241, 339), gave to the picture of maximum circulatory atonicity the name *hyposphyxie,* an expressive and easily understood term. Briefly, hyposphyxia is a modified form of asphyxia. The stimuli that regulate circulation, cardiac efficiency, and the blood-pressure are deficient; hence the circulatory mechanism lacks punch. This, it is believed, is due largely to a form of pluriglandular insufficiency in which the adrenal element is prominent.

From the standpoint of symptomatology it seems that this conclusion is perfectly reasonable. The principal clinical manifestations of hyposphyxia are: poor circulation with bluish-colored and cold extremities, cardiac asthenia and arterial hypotension, subnormal temperature, and evidence of stasis due to the slowed circulation. With these invariably go asthenia (due to poor cellular nourishment because of the bad circulation and, more important still, deficient hormone production with consequent reduced sympathetic function and generally slowed metabolism) and the usual findings of hypocrinism (65).

As a disease-picture per se, hyposphyxia is not common, because other conditions that so frequently accompany it are seen and treated rather than the hyposphyxia. I do not quite agree with Martinet that hyposphyxia deserves to be classified as a disease; but, as an extremely important syndrome which complicates so many chronic endocrine disorders, it is assuredly important and worthy of the intensive study and clinical appreciation that our French confrères have given it.

The treatment consists in reducing the insidious causative conditions, which through toxemia or in some other way have lessened the output of the hormones that regulate the circulatory department; the mechanical

removal of stasis by means of massage, exercise, etc.; the stimulation by means of homostimulative organotherapy of the glands that are largely at fault (whether as a cause or an effect); and good hygiene.

NEUROCIRCULATORY ASTHENIA—During the Great War a new term crept into the literature, "neurocirculatory asthenia." This indicated a picture essentially similar to the hyposphyxia already mentioned, which undoubtedly was due to the adrenal insufficiency following extreme stress and shock. It took some time for the endocrine aspects of this to be given their proper value, but Emile Sergent, of Paris, was indeed right in attributing it to hypoadrenia.

Neurocirculatory asthenia is another name for the neurasthenia and cardiovascular depletion already referred to in this chapter and elsewhere, *e.g.*, Hypoadrenia (35), Influenza (69), and Neurasthenia (77).

A comment from an old paper by Tom A. Williams, now of Miami, Florida (*Arch. Diagnosis,* Oct., 1915), pictures this depression thus:

"My object has been to show by these instances that when we are confronted with patients who have great asthenia, lack of concentration, and more or less of the long list of symptoms heretofore assigned to neurasthenia, we must not be content to stop with the latter as a diagnosis. If, in addition, there are low blood-pressure, subnormal temperature, and pigmentary changes, hypoadrenia may be the cause of the depression."

Fortunately, neurocirculatory asthenia is usually a functional difficulty, as I showed during the War, in my paper published in 1916 ("Shell-Shock and the Internal Secretions: With Suggestions as to Treatment," *Prescriber,* Oct., 1916, x, p. 203). The problem is inseparable from functional hypotension, to which attention is now drawn.

HYPOTENSION—Low blood-pressure is really a part of the Martinet syndrome. Since sphygmomanometry has become the rule, a great many cases of hypotension are routinely uncovered. Although quite overshadowed in clinical importance by hypertension, low blood-pressure is just as real a symptom as is high blood-pressure.

Hypotension must not be considered as a disease per se, but rather as a symptom indicative of other dysfunction. For example, nearly every case of hypotension has associated with it a noticeable lack of tone, which is either temporary or persistent. Low blood-pressure is common after acute infections such as influenza (69), and may occur as a result of anaphylactic, anesthetic, or traumatic shock. One expects to find it in drug addicts (75), and it is quite surprising how commonly it is associated with several chronic toxemic diseases as well as the constitutional endocrinopathies.

The essentially adrenal type of hypotension is, of course, of particular interest to us, and, as the reader will see elsewhere (69), many physicians have been directed to the study of adrenal function in their every-day practice as a result of their experience with postinfluenzal asthenia with its circulatory stasis, hypotension, and muscular atonicity.

There is no generally accepted etiological classification of hypotension. However, the unprecedented prevalence of low blood-pressure following the pandemic of influenza (1918-1919) prompted students of the subject to arrange a working classification as an aid to a better understanding of hypotension. The following etiological types suggest themselves:

Anaphylactic Shock causes a temporary lowering of the blood-pressure due to the presence of foreign protein poisons in the blood stream. The hypotension apparently is brought about by the accumulation of large quantities of blood in the splanchnic area and the large venous trunks, with a coincident lack of vasomotor tone.

Traumatic Shock, as a disease factor, was thoroughly studied during the Great War by English, French, and American commissions. Walter B. Cannon, of Harvard, who was a member of the American Shock Commission, states in his monograph on the subject that there is no convincing evidence that either the heart muscle itself or the nerve agencies controlling the heart exhibit any changes in shock that justify the conclusion that they are primary factors in lowering blood-pressure. However, the disturbance of the blood volume seems to have been proved to be the prime factor in the production of traumatic shock, including the associated low blood-pressure.

The Acute Infectious Diseases—influenza, diphtheria, scarlet fever, pneumonia, all of them except meningitis—show a coincident fall of the blood-pressure, which doubtless is the result of a vasomotor condition, perhaps even a paralysis, due to the action of the toxins produced by the infective organisms. The endocrine factor in the production of this symptom-complex is referred to again and again by European writers. Of these, Pende, Sergent, Lereboullet, Naamé, Scott, and others, assure us that many patients who die following these acute infections really succumb to the effects of the terminal adrenal involvement rather than to the original malady. (See p. 273.) There is a fundamental truth in the thought expressed most forcibly by Cannon that the adrenal secretion probably is the chief agent that enables the individual to meet successfully the great emergencies of life.

For more than twenty years America's greatest endocrinologist, C. E. de M. Sajous, of Philadelphia, insisted that the adrenals are concerned in the protection of the organism during infections and intoxications by contributing

an excess of their secretion during the early stage of the disease. This fact is now being accepted on all sides. After this stage of increased function is passed, the adrenals lapse into a condition of more or less temporary insufficiency through fatigue or exhaustion (35). This is well attested to by the many patients who, at the end of an infectious disease, instead of proceeding to a normal convalescence (48), remain in a sort of stationary subnormal condition characterized especially by muscular fatigue, cardiac and circulatory insufficiency, cold extremities, a lowered cellular chemistry, *and hypotension*—in a word, the fatigue syndrome.

The Chronic Infections are peculiarly common causes of hypotension. The subnormal syndromes that accompany chronic malaria, tubercle toxemia, or syphilis are illustrations of this. The exhaustion following repeated attacks of malaria, thoroughly studied by the Italian school, is always characterized by circulatory insufficiency and adrenal depletion. In fact, this is true of all the seriously depleting tropical disturbances.

Tropical Lassitude—From my own experience in the tropics, I should say that the feeling of excessive lassitude, the usual extreme lack of circulatory tone with not infrequent edema (at least in novices), and the defective alimentary tone, all point very clearly to an adrenal picture. I am quite sure that every time I have been in the tropics my circulatory capacity and blood-pressure were reduced. Naturally, persons who are forced to live in the tropics acquire a capacity to adjust themselves to the conditions there. But it is extremely unfortunate that the most customary means of attempting to overcome what might be called "tropical lassitude" is recourse to alcoholic beverages and stimulating foods, which often make bad worse.

In Syphilis, hypotension is often found in the secondary stage, and in all probability is associated with the frequently resulting aortitis. It is doubtful, however, if this explains the entire question satisfactorily, since here again the chronic poisoning, or the constant bombardment of the adrenals by toxic bodies incident to the infection, of necessity must reduce the capacity of these glands to act as detoxicating agents. In other words, an adrenal exhaustion occurs, such as has been emphasized in the consideration of adrenal dysfunction (35). There is a consequent lessening of the vasomotor tone, and hypotension is the net result.

Tubercle Toxemia is always present in varying degree in incipient tuberculosis, and a low blood-pressure is quite a constant sign of this toxemia. The asthenia usually gives the patient the first inkling that all is not well; indeed, it is of sufficient moment to lead him to seek medical advice. The

first endocrine organs to suffer in tuberculosis are the adrenals (94), for theirs is a vital detoxicating function, and the earliest evidence of adrenal depletion is the oncoming muscular weakness or fatigue.

Of all the toxemic states, Addison's disease is characterized by the most profound asthenia, with a coexisting hypotension—in my last case the systolic tension was 60 and the diastolic 35, if, indeed, this figure was correct. This is to be expected inasmuch as the adrenal glands themselves are the seat of the tuberculous lesion.

Functional hypoadrenia, then, must be conceded to be a most common cause of functional hypotension, and both the causes and the extent of its effects differ from the real addisonian picture only in degree. Physical examinations in such cases usually show no organic lesions. The symptoms commonly complained of are dizziness, headache, and mental and physical asthenia. There is lack of physical stamina; initiative and mental capacity are defective; the extremities are usually cold; gastro-intestinal complaints of the atonic type are common; and the blood-pressure is uniformly low, frequently below 100 mm. Hg.

Treatment should include much more than the attempt to support the depleted adrenal system. Adrenal support with either the adrenal cortex hormone or my-adrenal-spermin-thyroid combination usually raises the blood-pressure, but real satisfaction from such treatment follows only if the cause has been disposed of in the meantime. In the hypotension of postinfluenzal asthenia (69), the cause usually is a self-limited one; but if perchance there is a chronic focus of infection—teeth, tonsils, gall-bladder, appendix, etc.—the effect of the adrenal support will be limited in proportion to the extent and continuance of the adrenal depletion.

This is a good place to emphasize the reasons for the failure of this treatment to raise low blood-pressure when all the evidence points to the condition as an essentially adrenal depletion. I have encountered many patients with a blood-pressure of 90/60 or less in whom the foregoing treatment, in less than a month, caused an increase of thirty or more points (systolic), with corresponding euphoria. This improvement did not last, however, and before long they were as depleted and hypotensive as ever. In other cases, attempts to raise the low blood-pressure were not followed by even an initial response. What is the reason for this? The answer is one word—*stimuli.* The pressor endocrine mechanism, having been overstimulated, is depleted. The blood-pressure is reduced and, before it can be normalized again, the adrenals have to get on their feet. Obviously the best treatment is that which will lessen the stimuli, but unfortunately some of our habits interfere with the success

of this treatment. Stimulating drugs, such as strychnine, are distinctly contraindicated in such circumstances. The stimulating, putrefactive products from the alimentary canal must be disposed of. Above all, coffee must be proscribed because the principal reason for taking coffee is to secure the stimulus of the caffein. This interferes with the success of adrenal support to such an extent that many failures from this treatment have been traced to coffee alone.

MYOCARDIAL DISEASE—Considerable space has been taken for the discussion of the heart hormone (12) because this appears to be more than a physiological development. Despite several shortcomings in our knowledge, it seems undoubted that a cardiac extract may be used with advantage in certain types of heart disease in which myocardial degeneration is beginning. Many a clinical advance has antedated its physiological interpretation, and many an experience has been recounted that could not be explained readily.

After the completion of the experimental work that led to the discovery of the heart hormone, L. Haberlandt, of Innsbruck, began to use various products in a clinical way. In 1927 he expressed the opinion that ultimately this heart hormone would become available for therapeutic purposes and that, with this form of organotherapy, it would be possible to benefit at least some pathological conditions of the heart. It seems that this prediction is in a fair way to be fulfilled. One can readily see that a physiological heart remedy that constitutes a natural stimulant to weakened myocardial function would be superior to cardiac remedies now in use, which ultimately are always toxic.

More recently, K. Fahrenkamp, of Stuttgart (*Med. Klin.*, March 1, 1929, xxv, p. 338), reported his experience with Hormocardiol, a clinical preparation of Haberlandt's hormone, perfected in Germany. His investigations showed that, administered by mouth and by intramuscular injections, this product was tolerated by all patients without any by-effects. Strangely enough, the most benefit was observed in patients with angina pectoris. Clinical tests showed that the various digitalis glucosides cannot be replaced by the heart hormone. However, if the two remedies are given together, it is possible to diminish the total amount of digitalis given. Comparatively small doses of digitalis were effective in patients who had first been treated with the heart extract. Cases of severe decompensation are reported as responding promptly to its use. Instead of a bradycardia, there almost invariably followed a heart rate of ninety beats a minute. From experience to date, it is evident that this new organotherapeutic extract may eliminate the one undesirable digitalis effect hitherto accepted as inevitable. In cases

with an excessive heart rate, this product combined with digitalis restored a normal pulse instead of producing bradycardia.

Since the beginning of 1927 an American preparation concentrated from beef heart muscle has been available. This product, known as Myocardin,* is not the actually isolated principle, but four years' experience has shown it to be a clinically potent product. It has been used by several physicians who either were cardiopaths themselves or desired to test its possibilities in certain intractable cases. For instance, an Eastern physician employed it in a contagious-disease hospital, administering it to several children whose hearts were seriously compromised by intoxications due to diphtheria, scarlet fever, and other infectious diseases. The report showed clinical improvement and no cardiac incidents in the entire series.

A personal experience with Myocardin was recently related to me by a Philadelphia physician, who said:

"I must say that I am experiencing a wonderful improvement in general health. I do not pant for breath when I climb a flight of stairs, and do not have to rest until my breathing improves before I can go into the choir-loft. (I happen to be director and bass soloist of a choir.) The other day, I spoke to one of the specialists in Philadelphia about Myocardin, and told him that I had not taken any digitalis lately. My colleague tested my heart and said, 'Whatever you are taking, your heart is much better than it was three weeks ago.'

"At that time, my pulse had been very irregular and averaged only 52—now it is 62. I shall be grateful to you all my life for putting me in touch with Myocardin. I am quite sure that this preparation has enabled me to do things in my vocal and flute work that I have not been able to do since last August, when I was stricken with a heart attack in London and forced to go to bed for eight days. . . . "

There are many such reports, but as yet this method is in its clinical infancy. So far, it cannot be shown just how this heart extract causes the improvement that so often follows its use. Nor can it be said to be uniformly effective, for expected benefit may not occur in a case apparently similar to another that has responded well.

This heart muscle product seems to have several points in common with muscle extract—not heart muscle—which M. S. Schwartzman, of London, reported as being of value in myocardial disease and especially in angina and intermittent claudication.

Some comparative clinical studies were made by K. Fahrenkamp and H. Schneider, of Stuttgart (*Med. Klin.*, Jan. 10, 1930, xxvi, p. 48), between "the heart muscle extract previously believed by Haberlandt to represent a cardiac hormone [Hormocardiol] and an extract of voluntary muscle

[Carnigen] prepared so as to be free from albumin, histamine, and epinephrine." They found that the extract of voluntary muscle produces identically the same effects as does that obtained from the heart muscle. They therefore conclude that there is no evidence that the latter represents a true heart hormone. The action of both of these extracts, when administered orally under the influence of digitalis, is marked slowing of the ventricular rate in both fibrillating patients and those with sinus rhythm. Both extracts given either orally or intravenously to patients with recurring seizures of angina pectoris have controlled the attacks almost completely. In the presence of continued very high blood-pressure and insomnia, the prolonged use of these substances improves the patient's subjective symptoms and usually leads to a return of sleep. At present the dosage must be regarded as experimental. Patients with high blood-pressure usually show a fall of from 10 to 30 mm. of mercury, while those who are not hypertensive frequently show a transitory rise of about the same amount. (See *Am. Jour. Med. Sc.*, Aug., 1930, clxxx, p. 283.)

Georg Zuelzer, of Berlin (*München. med. Wchnschr.*, May 2, 1930, lxxvii, p. 760), also has developed an organic extract known as Eutonon, which exerts a hormone-like action on the heart, increasing the tone after a short preliminary diminution, and dilating the coronary vessels. In this respect it differs from Schwartzman's Myol, which is stated to produce a diastolic relaxation of the heart. The best effects in angina pectoris follow the combined use of Eutonon and a non-specific protein preparation.

The new pancreatic hormone or, as it has been called, "the circulatory hormone of the pancreas," has introduced the profession to still another measure and, as has been stated before (15), "has changed the therapeutic prospects in several of the stubborn cardiovascular difficulties."

Based on the last researches of E. Gley, of Paris, whose work along this line was interrupted by his death in 1930, a pancreatic hormone free from insulin and histamine has been isolated and called "Angioxyl." The Greek experimenter, N. Kisthinios, who for years was associated with Gley, has brought this work to fruition and with H. Vaquez and R. Giroux has reported some clinical possibilities which are not yet fully appreciated. Some of the case reports in their article (*Presse méd.*, Oct. 2, 1929, xxxvii, p. 1277) are quite remarkable:

"The first is that of a man 72 years old, complaining of retrosternal pain radiating into the left shoulder. The first signs of the trouble occurred fifteen months earlier, and at first they were noted only under the influence of effort, but for six months previously the attacks appeared also during the night and increased in intensity and duration, sometimes lasting as long as fifteen or twenty minutes. In January (1929) this man was overcome

suddenly by a most painful attack while descending from a train, and he was taken to a hospital as an emergency case. Here one of us was called in to examine the patient. He was in the midst of his anginal attack, of which he suffered from twenty-five to thirty crises during the day. The least movement caused the pain to return, and on two occasions this was accompanied by syncope. It was impossible to discover any valvular lesion. There was only an aortic clangor. The arterial tension was normal. A slight increase in the aortic diameter was noted and a considerable increase in its opacity. The patient was treated with Angioxyl, of which he received twenty injections, the first ten of twenty hypotensive units, the last ten of forty units each. After the sixth injection the crises ceased and the patient considered himself cured. Since the treatment was suspended on March 4, there has been no further attack. The improvement has continued. . . .

"The following observation refers to a man of the same age who for four years has had typical crises of effort angina, which have been more frequent and painful during the last four months. There was a systolic murmur at the base of the heart; arterial tension normal. On radioscopic examination, the left ventricle was found slightly enlarged, the aorta dilated and showing a marked shadow. He received fifteen injections of Angioxyl in twenty hypotensive doses during the first five days, and forty units during the ten days following. Beginning with the fifth injection, the suffering subsided and since then he has had no further attack.

"In these two cases the improvement was so typical and the evolution of the affection towards cure was so definite, that it seems that the attacks should yield in like manner to every other treatment, provided that it was administered methodically. Nothing could be more inexact, and here is the proof. A man 57 years of age has for years suffered from painful retrosternal crises, which occur on walking and are accompanied by the classical radiating pain. During the past eight months they have assumed an incredible intensity. Examination showed nothing remarkable except a slight increase in the aortic diameter and a considerable exaggeration of its opacity. However, it is important to note that this man had syphilis at the age of twenty, and had received very intensive treatment with mercuric cyanide, arsenobenzol, and bismuth injections for three years. Nevertheless, the pains persisted. In May, 1928, insulin was administered and with an entirely different effect. The patient was considerably improved, the pain occurred now only during rapid walking or immediately after meals; it was much less intense and no longer radiating. However, about two weeks after stopping the treatment, the pains returned with the same intensity. A second course of treatment brought a similar amelioration, which was followed in October by a further recurrence of the trouble. Between February 15 and March 3, 1929, we subjected this patient to treatment with Angioxyl, fifteen injections of forty hypotensive units. At about the eighth injection there was a notable diminution in the pain. With the tenth injection, the pain had ceased completely. On April 28 the patient reported that he had had no further trouble.

"It will be seen that here the recovery must be attributed to the pancreatic preparation, since specific treatment had failed entirely and insulin had been barely helpful."

Space forbids an extended consideration of the circulatory hormone from the pancreas. Angioxyl in France, Kallikrein in Germany, and Panocrin* in this country, are being used with increasing satisfaction, and withal an element of surprise—for "who would have thought there was another so potent remedy hidden in the pancreas?"

SYNCOPE AND SHOCK—In our consideration of Sajous' syndrome, "terminal hypoadrenia," the chief symptom is seen to be an ultimate degree of cardiovascular exhaustion (35). This picture, then, is really a maximum degree of hyposphyxia or a sudden and exaggerated neurocirculatory asthenia.

For years it has been known that adrenalin offers a life-saving service in shock and heart failure. The best method of administering adrenalin in cases of ordinary shock is by intravenous infusion of high dilutions in saline solution. Five drops of the standard 1:1000 adrenalin chloride solution to an ounce of normal salt solution dilutes the adrenalin to approximately 1:100,000, which is the proper strength to use intravenously. This solution is released in a slow, steady, continuous stream from a buret, to which a stop-cock is attached for regulating the flow.

This method is too slow, however, in profound shock and collapse, in which case the procedure described by George W. Crile, of Cleveland, should be resorted to. A cannula is inserted into an artery and directed toward the heart. From 15 to 30 minims of adrenalin 1:1000 is injected into the rubber tubing attached to the cannula as soon as the saline infusion begins. This immediately brings the adrenalin into contact with the larger arteries of the heart.

Since the posterior pituitary principle has been available, the credit has been divided between it and the adrenal medullary principle in the treatment of shock. As was originally shown by H. H. Dale, of London (1908), the principal value of preparations of the posterior lobe lies in their remarkable contractile influence upon unstriped muscle. This is especially evident in the control of the vascular musculature that is exercised by them in shock. Post-pituitary extract is the remedy *par excellence* in shock, since this condition is essentially a state of vasomotor paralysis and consequent reduced blood-pressure. Its power to contract involuntary muscle makes pituitary extract invaluable, for the accumulation of the blood in the large splanchnic veins is prevented in shock.

W. Blair Bell, of Liverpool ("The Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony, and Intestinal Paresis," *Brit. Med. Jour.,* Dec., 1909, ii, p. 1609), was the first to make a clinical study of this subject; and, while there are references to the experimental use of pituitary preparations before 1909 (it will be remembered that the tonic effect on the blood-vessels was described by E. S. Schafer and G. Oliver, in Edinburgh, as far back as 1895), Blair Bell deserves great credit for having given us the first clinical information on the subject. His conclusions regarding the applicability of Infundibulin in surgical shock, as well as in intestinal paresis and uterine atony, are generally accepted; in fact, no operating-room is now considered properly equipped unless a pituitary preparation is at hand to meet an emergency. Adrenal preparations have been quite superseded, at least in this particular condition, for pituitary extract causes a rise in blood-pressure fully as rapid as that produced by adrenalin. It has the additional advantages of greater safety and more prolonged action; for, while the influence of adrenal preparations is very transitory and is asserted by some to be followed by undesirable after-effects, that of pituitary is prolonged for hours and in proper doses is without the least danger. Twenty years ago, E. Bernouilli (*Cor.- Bl. f. schweiz. Aerzte,* 1912, xlii, p. 1149) prophesied truly when he expressed the opinion that

"It is possible that pituitary preparations, the stimulant action of which is less dangerous and more lasting, will [in shock and collapse] in the future replace adrenalin, to which will always remain the chief place as a local anesthetic and hemostatic."

TACHYCARDIA—Both hyperthyroidism and hyperadrenia cause marked degrees of heart-hurry or tachycardia. The heart muscle itself, as well as the nervous mechanism that controls it, is sensitized by these hormones. The physiology of muscle tonicity and that of the cardiac action constitute a subject too large to be more than reviewed here. In his "Text-Book of Physiology" (Philadelphia, W. B. Saunders Co., 1920, p. 344), R. Burton-Opitz outlines the generally accepted conception of this subject as follows:

"The functional capacity of the heart depends upon the tonus of its muscular elements. This fact implies that the latter are normally held under a certain physiological tension, *i.e.,* they are retained in a state intermediate between complete relaxation and contraction. The tonus, however, does not remain the same for a long period of time, but varies with the character of the internal stimuli. . . . This statement also applies to the arteries and other tubular organs, because their walls are ordinarily kept in a position intermediate between constriction and dilatation. . . .

"The nature of the stimuli upon which the tonus depends is still unknown. It is commonly held that the tonicity is due to the same stimuli that produce the contractions. . . .

"It must be clear that the tonicity of cardiac muscle furnishes a means of determining its functional capacity. Under ordinary conditions it is sufficient to note the amplitude and force of the contractions of the exposed or isolated heart, or to measure the pressure which the normally beating organ is capable of developing in the blood-vessels. . . . It must be evident that a loss of the relaxing power of the muscular units must place the heart under a certain disadvantage, because it lessens the capacity of its chambers. Quite similarly, it may be said that an unusual degree of relaxation must act unfavorably, because it tends to invite an undue distention and imperfect emptying of the cardiac chambers. The latter condition indicates a loss of tonus approaching fatigue, and may lead to a general dilatation of the organ called upon to perform an extra amount of work."

There is, of course, very much more to this. It may be said, however, that the nature of two of the unknown stimuli referred to is (1) endocrine and (2) sympathetic. The adrenal hormone continuously helps the muscle cells to detoxicate themselves, while the thyroid hormone stirs the sympathetic to activity. Therefore, *hypo*adrenia furthers muscular atonicity, and *hyper*thyroidism increases muscular activity, especially of the heart.

Our interest in tachycardia is to learn how to connect it with its cause and then to control it. If it is due to dyscrinism, three obvious procedures are called for: (1) the discovery of the endocrine cause, (2) its control, and (3) the sedation of the heart itself. As stated, hyperthyroidism is the best-known and most common cause of tachycardia. In fact, tachycardia is one of the sextet of clinical findings pathognomonic of the Graves' syndrome. The control of this cause is no sinecure, as will be seen, for it involves the discovery of the cause of the cause and this may be one or several toxic, emotional, or infective factors. Naturally this is a complicated problem that will test our mettle to the limit, as the reader will see (57).

The sedation of the heart itself must be considered under three heads: (1) The removal of stress, as already suggested, together with rest and such measures as spare the heart, chiefly hydrotherapy. (2) The encouragement of the muscle chemistry, through the adrenals, which appears to act upon the heart muscle itself. (3) Then come the pharmacodynamic heart remedies, of which digitalis is the best known.

One of the most interesting of the endocrine heart remedies is the cortical hormone, which has come into such prominence during 1930 and 1931. As we have seen (9), in normal physiology, this hormone is concerned almost solely with the regulation of muscular chemistry.

The effect of the standardized solution of Adreno-Cortin* on muscle detoxication makes it of value in a large series of conditions, acute and chronic, in which some muscular mechanism is in need of chemical regulation. The effect on the heart is both rapid and encouraging. The heart muscle, overburdened by the toxins of pneumonia, hyperthyroidism, and many other diseases, is clogged also with its own excessive cellular wastes due to the tachycardia. The cortical hormone is a catalyst to the chemistry in these muscle cells; therefore, it is a tonic, slowing the heart and at the same time apparently bringing about similar changes in all the muscles throughout the body.

Besides this general effect on the muscle chemistry, David Marine, of New York (*Am. Jour. Med. Sc.*, Dec., 1930, clxxx, p. 767), specifically credits the adrenal cortex with a service that he believes to be defective in hyperthyroidism. He says:

"A great number of glandular products have been used in the treatment of Graves' disease without much benefit. We have tried in an experimental way most of them, and so far have found only one that has any notable effect, namely the adrenal cortex. Ovarian and corpus luteum emulsions have a similar but less marked effect. In over fifty cases we have found that feeding a glycerin emulsion of very fresh ox adrenal cortex (glands from which 90 per cent. of medulla has been removed) causes a striking gain in body weight and in muscle strength. These effects quite constantly begin to appear after two weeks of feeding. . . .

"We think the adrenal cortex produces a substance that tends to regulate or control thyroid activity, which is deficient in Graves' disease, whereas the medulla produces a very powerful activator of the thyroid secretion which is not impaired in the developmental stages of the disease. . . . The most outstanding manifestation of Graves' disease is clearly a loss of control over the oxidation processes, and as a result of this there occurs a physiologic attempt toward compensation by an increased production of the thyroid hormone."

46. CHILDHOOD ENDOCRINOPATHIES

Fundamental Principles—Ateliosis—Athrepsia—Backward Children—Chorea—Cretinism—Cryptorchidism—Dwarfism—Enuresis—Infantile Hypoplasia—Minor Mental Defects—Mongolism—Progeria—Pubertas Præcox—Rickets—Spasmophilia—Spastic Paralysis.

THE VITAL nature of the hormones and the importance of the chemical messages that they carry are nowhere more obvious than in the study of the influence of the endocrine organs upon growth and development. There is perhaps no other field in which the application of organotherapy may be of such fundamental importance as in that of pediatrics. Nor are the prospects from endocrine therapy less wonderful to-day than in the past, for it was in this special field that scientific substitutive organotherapy was discovered—thyroid therapy for cretins (24).

FUNDAMENTAL PRINCIPLES—We have seen that it is necessary, in the clinical study of the disorders of one endocrine organ, to consider the others, for these glands exert a mutual influence upon each other. The effects of dyscrinism are more serious in early life, because so many functions depend upon the endocrines for their start. Endocrine changes should be recognized early, at or before puberty if possible, before the physiological habits become fixed and difficult to treat.

Although in many instances a syndrome may permit us to localize the primary and predominant pathological process in one of the glands of internal secretion, not infrequently we find cases in which the function of almost all these glands is simultaneously disturbed. We may also note symptoms caused by a particular gland that are due to compensatory reactions to the original imbalance. Every abnormal child requires individual study. In other words, we must generalize the disease and individualize the patient. The practitioner who, after finding certain symptoms and physical signs, concludes that the case belongs to a class of diseases—that is, the physician who individualizes the disease instead of the patient—will ultimately fail in his purpose. Undoubtedly this explains many unsuccessful experiences reported by those who oppose organotherapy. Instead of practising it judiciously, they too often abuse its administration.

We must be careful not to label every abnormal state an endocrine disturbance and thus convert the whole subject into a present-day fad. There are many pathological states independent of endocrine involvement—contagious and infectious diseases, various parasitic diseases, ordinary malnutrition, vitamin deficiencies, etc.—which require other therapy. But the endo-

crines may often be employed advantageously with the vitamins or indicated drugs in the conditions referred to in this chapter.

Let us treat the dyscrinisms with organotherapy supplemented with other indicated therapy, and let us treat the other disorders with indicated therapy supplemented with rational endocrine support. *A child cannot go through serious illness with the endocrines unscathed!*

ATELIOSIS—This is a rare form of pluriglandular diminutivism in which the child is normal mentally, the secondary sex characteristics develop moderately, and eventually maturity and even fecundity is reached. This dwarfism is the so-called "Tom Thumb" type, which is seen more often in circuses and midget theatrical troupes than in consultation.

Although development sometimes proceeds to a point where procreation is possible, delivery can be accomplished only by the cesarean operation. Midgets not infrequently produce normal children.

ATHREPSIA, marasmus, or malnutrition, is one of the serious nutritional disorders in infants that deserves consideration from an endocrine aspect, although the endocrine involvement in the majority of cases is secondary.

The thymus of the marasmic baby is usually abnormally small, and I have found that substitutive organotherapy gives good results. Thymus gland substance, combined with thyroid, improves the ability of these infants to absorb and assimilate their food, though some cases resist all forms of treatment.

The hypoadrenal type of malnutrition shows itself in the pale, emaciated, tired, mentally sluggish child whose blood-pressure is low, appetite capricious, asthenia marked, and extremities are cold. These little patients often suffer from nephritis as a result of the accumulated wastes. Suitable organotherapy, good food, and enforced rest, frequently prove beneficial.

In the lymphatic type of malnutrition the lymphatic tissues are definitely involved. These patients appear undernourished, underfed, and phlegmatic. Their breathing resembles that of asthmatics, and they are subject to various blood and lymphatic dyscrasias as well as to tetany and convulsive seizures. The lymphatic glands, tonsils, and adenoids frequently are enlarged. This picture characterizes a pluriglandular disturbance involving the endocrines and the hemopoietic organs, and therapy is directed at the most obvious phases of the symptomatology.

Maximal thyroid insufficiency also produces a certain type of malnutrition in infants—the inert, listless, constipated type. They are benefited by the long-continued use of thyroid in gradually increasing doses.

BACKWARD CHILDREN—This term covers a wide range of disturbances, the present consideration of which necessarily must be fragmentary. Most important of the glands that control growth and mentality is the thyroid, its influence on development being paramount. The thyroid aptly has been called "the keystone of the endocrine arch." Its relation to developmental dystrophies in children has been studied more than that of any of the other endocrine organs; the literature is tremendous. The thyroid feature of the disorder underlying the syndrome seems to have overshadowed the associated factors. Just because we realize the importance of the rôle played by the thyroid, we should not neglect the rest of the cast. The support that the thyroid receives from the pituitary—especially the glandular (anterior) lobe—and the thymus, is essential. Later, as the endocrine influences of the gonads replace those of the thymus, the reciprocal relation between the sex glands and the thyro-pituitary mechanism is of extreme importance. In reporting the histopathological changes observed in two Mongolian idiots, Murray B. Gordon, of Brooklyn (*Endocrinology,* Jan.-Feb., 1930, xiv, p. 1), remarked that not only was the thyroid gland affected in each patient, but the other glands also were the seat of pathological changes.

Although we may be sure that the backward child invariably has a thyroid defect, the associated glands, especially those mentioned, deserve consideration. The logical conclusion is that pluriglandular treatment is preferable.

The differentiation between those defective children who are likely to respond to organotherapy and those in whom there is no likelihood of benefit is very difficult; and it is a very serious thing to doom a child to lifelong disability by saying that this or that method of prospective merit need not be employed because it *may be* useless. The determination of cerebral difficulties is often an obstacle. If there are definite changes in the cerebral cortex, or if there are developmental defects in the cranium that would influence cerebral growth and function, the prospects obviously are not good; it is for this reason that many idiotic children are quite hopeless. The hypocrine child, on the other hand, is merely sluggish—not idiotic or demented—and his physiology is retarded. That growth is not permanently arrested has been proved by the fact that thyroid or other glandular therapy produces a complete change in the clinical features.

There is always the possibility, however, that even in the child who is definitely defective from a cerebral standpoint there may be enough associated functional irregularity to warrant an attempt to modify it. Surely it is more reasonable to attempt organotherapy in such cases than to deny the child and his parents this last chance.

The signs of dyscrinism are not marked in the young, except, of course, in cretins and Mongols. In the diagnosis of dyscrinism it is important to review the incidents of the developmental years, noting the occurrence of severe infectious diseases or other prostrations, the rate of growth, the time of walking, of cutting the teeth, of puberty, and other significant features. The criteria of abnormality are often found in these factors. Thus we may see in retrospect the onset of abnormal metabolic changes, the development of endocrine imbalance from toxemias, etc., which may lead to a complex that offers prospects of control only by measures calculated to reestablish a more nearly normal function of all the endocrines.

The oral administration of pluriglandular therapy to defective children has been more successful in my experience, and in that of a good many of my friends, than thyroid, pituitary, or thymus feeding alone—all of which have been recommended time and again in the literature. I have therefore used a combination of these preparations as follows: 2 gr. of desiccated anterior pituitary, 1 gr. of thymus, 1/12 gr. of thyroid, with the mineral salts corresponding to those found in the blood as the excipient. This is known as Antero-Pituitary Co.*

The usual dose of this formula is 2 or 3 tablets a day, the former for children under four, and the latter for older ones. I prescribe the tablets for four out of every five weeks, and advise that they be continued for a minimum of six months. It is useless to begin treatment unless the parents promise to continue it for this length of time. The real attempt in these cases is to reestablish the deficient functions, to educate certain glands; and, as with all other forms of education, it takes time. This formula must be given regularly, the results watched carefully, and, if necessary, the treatment modified to suit the changing conditions. Every associated measure to further the desired outcome should be advised. Particular attention shoud be paid to elimination, to the simultaneous use of vitamins (101), and to the metabolism of the mineral salts (100).

The following case report, by M. J. Konikow, of Boston (*Endocrinology*, March, 1922, vi, p. 218), is given here because the mental backwardness of this patient overshadowed the physical stigmata, and the purely developmental aspects were such as to make the prospect of benefit less encouraging. Then, too, my own formula was used:

"This is the case of A. F., a girl of fourteen, of healthy parents, and whose birth was normal. When a year old she had convulsions that came on an average of twice a year until she reached the age of six. Then the convulsions ceased. Measles and tonsillitis were the only diseases the child had gone through. Though her physical development up to about two years ago was

apparently normal, her mental development caused her parents considerable anxiety. It took her eight years to complete the first five grades of school, she being obliged to remain two years in each of the last three grades. A tonsillectomy and adenectomy were performed with the view of raising her intellect, but without perceptible effect on the patient. Her growth during the last two years was suddenly very rapid; and she became tall and lank, but her mental capacities either remained stationary or developed very slowly. She lacked concentration—she often returned her library books without reading them. Broken dishes and faulty chores were the despair of her parents.

"With such a history this girl came under my observation on September 27, 1920. The following data were obtained: The girl was tall for her age and weight, measuring 62 inches in height and weighing 86.5 pounds. She had long arms, large hands, long fingers, long legs, and large feet. Otherwise, physical examination was negative. Her mentality corresponded approximately to that of ten years. At the time of my first examination the patient was in the fifth grade, this being her second year in the same grade. The patient was given capsules three times a day, containing the following formula: pituitary gland (anterior lobe), gr. ii; thymus gland, gr. i; thyroid gland, gr. 1/12; calcium phosphorus compound q.s. ad. gr. v.

"With the exception of two months, March and April, 1921, the patient was taking these capsules regularly from October, 1920, to July, 1921. In March and April she ceased to take them because her brothers teased her, implying that her 'wisdom' and smartness came from these capsules.

"With this in view, it is interesting to study her school card, which was marked bimonthly. It is seen from this card that her November and December record was a great improvement over the one for September and October, while the January and February record showed a still further advancement. The March and April record was quite in accord with the omission of the capsules during these months, while the resumption of these capsules during the months of May and June resulted again in a considerably improved school record.

"On February 11, 1921, her height was 63.5 inches; her weight was 92 pounds; her span (from middle finger to middle finger), 63.5 inches; her pulse, 80; blood-pressure, 60/100; secondary sex characteristics (enlargement of the breasts, growth of pubic and axillary hair) present.

"On November 6, 1921, the following data were obtained: Height, 64 inches; weight, 98½ pounds; span, 64 inches; blood-pressure, 50/110; pulse, 80. Her first and only menstruation occurred two months ago."

Although my own work has stressed the importance of pluriglandular therapy, the idea is not original with me. Claude and Gougerot, of Paris, uncovered this great advance in organotherapy in 1907 (5). While I believe that my formula, Antero-Pituitary Co.,* was the first preparation of its kind to be recommended in this country, it was by no means the original endocrine formula suggested to replace thyroid alone or to supplement it. As far back as 1912, R. Dupouy, of Paris (*Jour. de méd. de Paris,* 1912,

xxiv, p. 87), who had made an extended study of the treatment of backward and defective children, used pluriglandular therapy with very encouraging results, which he summarized as follows:

"(1) A rapid increase in stature, which had been slow to show itself with thyroid treatment, and a reduction in the rapid growth in those who seemed to be suffering from gigantism. (2) A less marked reduction in emaciation than with thyroid treatment alone, and a more decided tendency to regain the initial weight than when thyroid alone had been allowed. (3) An extraordinarily rapid modification of the urinary elimination, clearly indicating that metabolism is reestablished on a more nearly normal basis and that assimilation has become regular. (4) A beneficial effect on the disorders which are found in the backward (and which thyroid treatment often does not influence), including troubles in vision, incontinence, visceral ptosis, umbilical hernia, etc. (5) A general physical metamorphosis and reestablishment of the sexual functions (menstruation, ovulation, etc.). (6) A psychic and sensory metamorphosis and a reduction of asthenia and excitability, as well as a noticeable progress in the intellectual capacity, thus allowing these unfortunates to take their proper places in society."

If there is a possibility that such a list of ameliorations can be obtained from pluriglandular therapy, then a very good case has been presented for it, and it merits more extensive use in the treatment of these conditions.

The trend toward the pluriglandular treatment of complex endocrine disorders is increasing. Harvey G. Beck, of Baltimore (*Bull. Univ. of Maryland School Med.*, April, 1929, xiii, p. 185), says:

"One should like to know the effect of anterior pituitary alone. My personal feeling is that it was largely responsible for the results obtained. However, there is very little doubt that thyroid in some manner augments the effect of the pituitary substance. Just how, no one can be certain from our present knowledge. . . . The effect of anterior lobe pituitary feeding is apparently enhanced by the addition of small doses of thyroid, especially in the reduction and redistribution of fat. . . . It [anterior lobe] has the effect, especially when combined with thyroid, of restoring normal mental function in mentally defective children in cases of dystrophia adiposogenitalis."

CHOREA—The peculiar spasmodic, hypertonic disorder that bears the name of St. Vitus, the patron saint of New York (!), is beginning to be considered as an essentially endocrine toxemia. There are a number of clinical similarities between chorea, tetany, spasmophilia, and hypoparathyroidism. In view of the fact that chorea commonly occurs in children at or near puberty, when endocrine stress is great, and in view of the fact that it may follow a severe rheumatic infection, which certainly may and does affect the endocrines, many physicians have treated chorea as a form of

parathyroid insufficiency. In this connection, it will be interesting to read the information made available about tetany (81).

There are a number of published reports of encouraging clinical experiences in the treatment of chorea. I, personally, have met a number of physicians whose use of various parathyroid measures in the treatment of chorea has been most pleasing.

In the five-volume work, "Endocrinology and Metabolism" (Barker, Mosenthal, and Hoskins, New York, D. Appleton & Co., 1922, Vol. I, p. 700), Haberfeld's report of the anatomical findings in the parathyroids in two cases of chorea minor is referred to. There was a fresh hemorrhage of the parathyroids in one case, and marked congestion in the other. It was suggested that "these changes pointed to a possible relationship of chorea minor to lesions in the parathyroids."

An Italian physician, Di Pace (*Folia med.,* Feb. 28, 1925, xi, p. 154), reports the case of a girl of fifteen with chorea minor, which occurred without any previously known cause and did not respond to several of the customary forms of therapy. A complete cure, which at the time of the report had lasted more than four years, was brought about solely by parathyroid therapy (fifteen intramuscular injections and a suitable product by mouth for only a month).

Another Italian physician, V. Arancio (*Terapia,* Aug., 1926, xvi, p. 234), claims that parathyroid extract has "a decisive and rapid effect in most cases of Sydenham's chorea," that severe and long-resistant attacks may yield to it rapidly, and that the benefit usually is permanent.

An Indian author (*Indian Med. Rec.,* Dec., 1925, xlv, p. 384) reports a case of chorea in a girl of fourteen, in which parathyroid by mouth "brought about a complete cure in forty days." This cure has persisted after two and a half years. Another girl of fifteen received parathyroid both by injection and by mouth, and, at the time of writing, the cure had lasted eight months.

There is surprisingly little on this subject in the medical journals of this country. However, in the *Journal of the American Medical Association,* for March 17, 1928 (xc, p. 889), reference is made to a girl of twelve with an acute chorea, who had failed to improve following rest in bed, a milk diet, and a solution of arsenous acid. The author remarks:

"When given parathyroid extract she improved rapidly, and the cure was complete in less than a month."

There are several standardized parathyroid solutions that may be given by intramuscular injection—Parathormone, Paroidin, and Paracalcin.* The dose is from 10 to 20 units, from ½ cc. to 1 cc., daily for ten days, preferably

accompanied by oral parathyroid therapy. The parathyroid formula containing spleen also—Para-Spleen Co.*—has been given by mouth to many choreic children, whose physicians consider it a helpful measure.

CRETINISM—Athyroidia or thyroid atrophy originating in utero or in earliest infancy causes a quite typical endocrine picture. The stigmata include stunted growth, defective development, delayed mentality, and backwardness in sitting up, walking, and talking. The face is puffy, the lips and tongue are thick, the skin is rough, the teeth are decayed, the nails cracked, and the hair is dry and brittle. The pot-belly is typical, and there is a general appearance of infiltration and unhealthiness.

Some day, prophylactic treatment of the pregnant woman will be the rule, and it should do more good than late attempts to cure the child, which is just as impossible as to "unscramble eggs." Prophylactic treatment includes organotherapy and some form of iodine (84).

The cretin responds to organotherapy as by a miracle, even though the best results may leave much to be desired. Every one of the stigmata is gradually modified. Thyroid extract is a true specific for athyroidia. But, because the thyroid gland encourages all the other endocrines, a cretin is always deficient in other glandular functions also. Therefore, it is both theoretically and clinically possible to accomplish more with pluriglandular therapy than with thyroid alone.

The routine suggested is the Antero-Pituitary Co.,* already referred to, with "enough" additional thyroid. Prescribe 1 sanitablet at meals t.i.d., for four out of every five weeks indefinitely, plus variable amounts of Endothyrin*—from ½ to 2 gr. a day—using the response of the patient as an indicator of the dosage.

CRYPTORCHIDISM, or delayed descent of the testes, is a stigma of a developmental defect that is commonly related to endocrine shortcomings. The subject is mentioned here merely for record as a "childhood endocrinopathy." In Chapter 58 there is some further information.

DWARFISM—The arrangement of this book makes it necessary to scatter the references to the different types of dwarfism. Achondroplasia is given a chapter by itself, chiefly because it is not known to be an endocrine disorder (33). Ateliosis has been referred to in this chapter. Dwarfism, being essentially a bone dystrophy, is considered in that category (41). Hypoplastic dwarfs (Timme) are thymus cases (93). Finally, there is the important Lorain-Levi type of dwarfism, which is believed to be caused by hypopituitarism, and is considered in the chapter on Pituitary Diseases (83).

ENURESIS—Nocturnal enuresis in children is often an endocrine problem. While its etiology is not definitely established, there is reason to assume a possibly inherited upset of the sympathetic nervous system. It was Leonard Williams, of London (*Lancet,* May 1, 1909, cxvi, p. 1245), who first emphasized this and reported a case of enuresis in a 9-year-old boy in whom he tried removal of the adenoids. The operation made the boy much worse, however; and, believing that the removal of the adenoids deprived the boy of a necessary internal secretion, he then gave him thyroid extract, ½ gr. twice daily. The result was instantaneous and complete, with no further bed-wetting. Twenty-four other cases were treated similarly, only one of which proved refractory to the treatment. Of course, thyroid treatment is likely to be effective only in the presence of hypothyroidsm.

The idea that hypothyroidism can cause frequent micturition has seemed strange to some, but it is true nevertheless. The explanation is that hypothyroidism causes infiltration of the bladder walls just as it does of other structures (67). Because of this, the external layers of squamous epithelium are more easily desquamated, thus causing irritability due to the sensitiveness of the denuded bladder walls.

Another purely empirical organotherapeutic measure that has been used in certain cases of enuresis, is a series of injections of posterior pituitary extract. Such treatment has been surprisingly successful in some instances, but the reason for the prompt benefit is not so clear. It has been suggested that it may be due to its musculotonic effect upon the sphincters.

The following routine is one that I am in the habit of recommending for the control of nocturnal enuresis in children:

First, rule out external irritating causes such as adherent prepuce or clitoris, pinworms, etc.

Second, proscribe all liquids after 4:30 P. M.

Third, step-ladder thyroid therapy thus: Prescribe 45 tablets of Endothyrin,* gr. ½; give half a tablet a day for a week; during the second week, give a whole tablet daily; during the third week, 2 tablets daily; and during the fourth week, 3 daily. If, at the end of this time, there is no marked change, then,

Fourth, give intramuscular injections of Liquor Pituitarii (Obst.) daily, starting with ½ cc., containing 5 international units, and gradually increasing the dose until 10 injections have been given, the last one being 1 cc. of the surgical strength, containing 20 units. If no improvement follows these two diagnostic-therapeutic procedures, the cause of the enuresis is probably not an endocrine one.

INFANTILE HYPOPLASIA—Status hypoplasticus, or Timme's syndrome, is a childhood nutritional hypocrinism that interferes with growth and sexual development. It differs in a number of respects from infantilism, for the thymus is always large. It is suggested that this hypoplasia is caused by the interference of the thymus with the normal course of endocrine development. It is really a result of the so-called *status thymicolymphaticus.* Since this is considered elsewhere (93), it must suffice here to say that some cases respond to the persistent application of the indicated endocrine treatment.

MINOR MENTAL DEFECTS—Supplementing the suggestions made earlier in this chapter, a few words are added here regarding the child who is in apparently normal health, but who is slowly falling behind in his school work.

Since it has become possible to determine a child's intelligence quotient so efficiently and accurately, some public school systems are attempting to take care of the mentally retarded child. School nurses and physicians have become just as important as the teachers, and they are doing their best to exclude adenoids, diseased tonsils, excessive myopia and all errors in refraction, astigmatism, defective hearing, malnutrition, etc.

But there is still a great need; and I venture to say that there is a large percentage of children, who, by proper treatment, could be enabled to progress much faster than they are. These are not really mental defectives, but mental invalids. They have the same opportunity to attain mental normalcy that any sick child has of being brought back to health by correct treatment.

A very interesting report of "Endocrine Studies of the Children in Special Schools," by C. J. Marinus and O. P. Kimball, of Detroit (*Bull. Wayne Co. Med. Soc.,* Jan. 7, 1930, xxi, p. 3), shows that 17 per cent. of the children in the Detroit special schools are endocrine problems. This may not appear to be a very large or alarming percentage, but when it is realized that, according to these authors, "many of these can be prevented," the import is evident.

After ruling out those whose defects were attributable to foci of infection, defective hearing, impaired eyesight, etc., these workers had a class of 766 mentally backward children whom they termed as "special study or endocrine problems." Those who were principally endocrine were classed as follows: Mongolism, 3; albinism, 1; microcephaly, 3; cryptorchidism, 5; glandular dyscrasias, 495; pituitary dysfunction, 213; thyroid insufficiency and endemic goitre, 282.

Why should more than seven hundred children be classed as "backward" and merely be placed in special classes, if it is possible to normalize some of them by also adding the indicated medical care?

Another interesting statistical report comes from A. W. Rowe, of Boston (*Sc. News Let.*, Feb. 28, 1931, xix, p. 137), who studied a group of 650 children in whom 104 were shown to have behavior difficulties. Nearly two-thirds of these 104 children had some endocrine abnormality. It was believed that the pituitary was at fault in seventy, and in practically all the remaining thirty-four the thyroid gland was involved. Indicated organotherapy not only caused improvement in the general health, but made decided differences in the behavior of some of these children.

Some day we shall have a Department of Health in this country and then as much or more attention will be paid to backward children as is now so aggressively given to the development of milch cattle or fancy hogs; and, as with these animals, not all the efforts will be confined to the offspring, either.

MONGOLISM—Mongolian idiocy or Mongolism is an endocrinopathy occurring in infants and young children, with which there are associated certain mental and physical stigmata including a Mongolian cast to the features. The cause is unknown, but Mongols are probably defective from both the thyroid and the anterior pituitary aspect. In fact, ten years ago, Walter Timme, of New York (*Arch. Neurol. and Psychiat.*, May, 1921, v, p. 568), reported that in twenty-three of twenty-four non-selected cases of Mongolian idiocy, the sellar radiographs

". . . showed a peculiar change from the normal in the anterior portion of the *fossa pituitaria*. This change consisted in an excavation under the anterior clinoid processes. . . ."

In connection with this quite uniform but not necessarily pathognomonic pituitary change, the associated manifestations of dyspituitarism are of special interest. Again, quoting from Timme (*loc. cit.*):

". . . among the clinical signs of Mongolian idiots we invariably have the combination of subnormal and disproportionate body growth coupled with lack of genital development. Thus in boys undescended testicles are quite frequent and in girls abnormalities of the genitals with tardy menstrual flow or even complete amenorrhea are the rule. The intimate relationship which in early life exists between the anterior hypophyseal lobe and the pharyngeal glandular elements is also strikingly coincidental with the extreme pharyngeal mucous secretion seen in Mongolian idiots."

Although the actual extent and character of the dyscrinism varies, it is permanent. Therefore, Mongolism practically never is controlled com-

pletely; however, improvement of a most encouraging nature is possible. Children may learn to sit up at two or three years, to walk at five years or older, and to talk after a fashion at nine. (These developments have occurred in patients whom I have treated personally.)

In 1928 Timme discussed Mongolism quite thoroughly before the American Association for the Study of the Feeble-Minded. In his opinion, the principal manifestations of Mongolism are the result of faulty development, or lack of development, of the anterior lobe of the pituitary. He reported on the treatment of a number of Mongoloid patients with various pituitary preparations, including whole gland and the anterior lobe. These substances were given both by mouth and by injection, and, as the record reads, "In addition the patients have been given the usual thyroid treatment." According to this eminent endocrinologist:

"As a result of ten years of this work, I have brought many of my Mongoloid patients to much higher levels than we have heretofore been able to do. Some of these children who were faced with the prospect of remaining virtual idiots, unable to talk properly, dress themselves, or even eat like normal children, learned to do arithmetic up to multiplication by three or more figures and long division. They also learned to write letters and do oral arithmetic, which is a remarkable achievement for these cases."

Ordinarily the physical stigmata, of which the Mongolian facies is the most important, do not change as improvement occurs in other phases, but in Timme's paper there is a photograph of a 15-year-old boy "with hardly a trace of his original characteristics present." One 8-year-old boy described in Timme's communication has actually attained an intelligence quotient of 90 per cent., which has, indeed, brought the child up to the average. He was on organotherapy for seven years.

The therapeutic procedure followed by Timme should be outlined here, for his work in this field is outstanding. His routine is (*Proc. Am. Assn., Study Feeble-Minded,* 1928, 52nd year):

Thyroid (B. W. & Co.) from gr. 1/10 to gr. ¼ daily; sodium iodide, saturated solution, two drops daily; and pituitary substance (Armour), one capsule containing from 1 to 2 gr. anterior lobe, and from 1/10 to ¼ gr. whole gland—a capsule two or three times daily, three hours after meals. Later on, hypodermic injections of antuitrin (P. D. & Co.) are given; ½ ampule twice weekly may be added. As the child grows older, all of these are gradually increased to tolerance limit, and the antuitrin to one whole ampule three times a week.

My own treatment of these cases always starts with the routine outlined on page 352. It is as difficult to differentiate the endocrine values in Mongols as in any other type of dyscrinism. Later, additional pituitary is often given

either as Accretin* (18) or the desiccated anterior lobe, both the dosage and the form being changed to fit circumstances. I never advise hypodermics in children who must continue the therapy for years.

It appears that endocrine therapy kindles a previously missing spark, which must be fanned into a flame by individualized education and suitable environment. The more or less mechanical type of institutional care does not compare with individual attention and education. It is unfortunate that so many of these children are, so to speak, elbowed to one side and pushed out of the procession. Clinical experience over a period of twenty years convinces me that the collective care of Mongolian defectives, *i.e.*, their treatment and education in schools and institutions, falls short of what might be accomplished because of the lack of individualized attention, which is so important.

PROGERIA—One of the strangest as well as the rarest of the endocrine mysteries is a peculiar combination of infantilism and senility. This condition was originally described by Jonathan Hutchinson, of London, and has since been interestingly discussed by Hastings Gilford, of Reading, England, who gave it the name "progeria." He considers it a senile involution affecting an organism that has not fully developed, upon which is superimposed an atrophy or sclerosis of the endocrine glands.

This extremely infrequent difficulty is certainly a childhood endocrinopathy, for it causes an astounding degree of mental precocity and physical senility before puberty. Children with progeria are old before they are grown up—wrinkled, and definitely senile.

According to H. Zondek, of Berlin ("Die Krankheiten der endokrinen Drüsen," Berlin, Julius Springer, 1926, p. 227), it is hardly reasonable to hold any one endocrine gland completely responsible for this condition. In his opinion, the clinical picture of presenile involution is a syndrome of maximal pluriglandular insufficiency. Frequently, there is atrophy of several glands, though the most prominent defect is probably in the adrenal cortex. Several writers have incriminated the thymus, the thyroid, and the anterior lobe of the pituitary gland.

Progeria is really a medical curiosity, which is diagnosed purely clinically. The endocrine findings are quite indeterminate, and there is no treatment.

PUBERTAS PRÆCOX—A condition of abnormally early puberty is known as pubertas præcox or macrogenitosomia. Fortunately it is rare, since it is practically always the result of neoplastic changes in the pineal gland or the adrenal cortex. The subject is briefly considered under the heading, Hypergonadism (58).

RICKETS—Rachitis is a nutritional defect occurring in childhood. It undoubtedly is also an endocrinopathy, but more often it is considered as a bone dystrophy or an avitaminosis. It is discussed more fully in Chapter 41, but opportunity is taken here to warn the reader never to fail to study the endocrine aspects of *all* children who are suffering with disorders of nutrition.

SPASMOPHILIA—A series of clinical pictures in infants—including muscular hypertonia and convulsions, or a tendency to more or less serious convulsive manifestations such as laryngismus stridulus, tetany, etc.—have been classed as spasmophilic in character, and the term "spasmophilia" has come to include them all.

Spasmophilia is a tendency toward sudden convulsive explosions of muscular energy varying in degree and toxic in character. These are always followed by a period of profound depletion or exhaustion, with stupor, loss of consciousness, and even death.

Although spasmophilia originally was considered to be of central nervous origin, opinion is now veering to an endocrine conception of its etiology. The nervous features are, of course, very real, but the nerves are merely the channels through which a deranged chemistry affects the muscles. We do not know what upsets the chemical balance, but the parathyroid glands apparently are involved just as they are in parathyroid tetany.

Whether the soil that facilitates the spasmophile diathesis is disturbed by hypocalcemia and the concomitant hypertonia that one expects in such circumstances, or whether it is deranged by the guanidine-like protein derivatives such as are in excess after parathyroidectomy, is not known; but there is an increasing number of clinicians who are recommending parathyroid in the treatment as well as the prophylaxis of spasmophilia.

For instance, in his book on "The Parathyroid Glands in Relation to Disease" (London, Edward Arnold & Co., 1924, p. 45), H. W. C. Vines, of Cambridge, says:

"In spasmophilia there is stronger evidence of parathyroid dysfunction [than in epilepsy]. Clark records three cases of this condition treated successfully by parathyroid feeding, and Frank, Stern, and Nottmann consider that symptoms of spasmophilia are accurately represented by mild intoxication with methylguanidine. Calderin produced convulsions in guinea-pigs by injection of 1/1000 potassium oxalate, and found that the intravenous injections of parathyroid extract brought about immediate relief. From these experiments he considered that laryngospasm in infants was due to a default of calcium metabolism and was, in fact, a manifestation of spasmophilia; in eight cases of laryngospasm he obtained successful results with parathyroid

therapy. Other investigators have found a reduction of the blood calcium in spasmophilia, so that there seems to be justification for associating the condition with parathyroid hypofunction."

Save only in the treatment of tetany, the administration of parathyroid extract to small children is best spread over a period of several months. During the first two or three weeks of treatment a series of intramuscular injections of standardized parathyroid solution (Paracalcin,* Parathormone or Paroidin) is given, usually 10 units daily or every other day. The parathyroid concentrate is also given by mouth throughout, in doses of gr. 1/20 to 1/10 b.i.d. The oral therapy is continued for a long time after the injections. My formula, Para-Spleen Co.* (one tablet, t.i.d.), is preferred by many pediatrists, and may be used in the entire list of hypertonic and hypercalcemic disorders of children discussed in this chapter.

SPASTIC PARALYSIS—Another pediatric use for parathyroid therapy is being developed at the Orthopedic Hospital in Los Angeles. Based on its known sedative influence in the hypertonic type of muscular disorders such as those outlined previously, parathyroid has been used by Clifford A. Wright and his associates as a symptomatic remedy in children with spastic paralysis. Doses as large as 1 gr. three times a day have been given. The results in several hundred cases are unusually encouraging and may lead eventually to a recasting of our conceptions of the factors underlying this disease.

47. COMMON COLDS

THERE SEEMS to be a special relationship between the toxic aspects of the every-day cold and endocrine disorder. Besides coryza, headache, and malaise, there is often a marked achiness and tiredness—symptoms similar to those that we credit to endocrine dysfunction due to more serious acute infectious disease, as, for example, influenza (69).

In many cases, a common cold seems to be more than an acute infection of the upper respiratory tract. Everybody knows that certain persons are especially susceptible to drafts and cold; they are "always catching cold." In such cases, the infection itself cannot be the only factor; perhaps it is not even the most important one, for the same germs, in the same room, may produce a cold in one susceptible person while others who "never catch cold" are unaffected.

In his paper, "Endocrine Factors in Common Colds" (*Clin. Med. and Surg.*, March, 1930, xxxvii, p. 179), James H. Hutton, of Chicago, says:

"Three endocrine glands are frequently involved in colds: the thyroid, the parathyroids, and the ovary. The pituitary may be involved, but less frequently. The pituitary seems especially susceptible to mumps and whooping-cough, as is shown by the frequent stoppage of growth in stature and the development of obesity of the girdle type, following such infection."

It is surprising how menstrual disorders cause a susceptibility to colds in certain women. Many times the customary premenstrual upset is the deciding factor, for, in the presence of the other usual causes, the patient catches cold during this period of depletion. This may even predispose to tuberculosis as will be seen elsewhere (94).

In these cases, of course, the dysovarism is but a part of a larger picture; and the strain put upon the thyroid, pituitary, and adrenals because of the ovarian necessities detracts from their other services (80). Obviously the treatment of a condition like this should include the regulation of the dysovarism. In fact, in some persons this susceptibility to frequent colds is controlled only when the endocrine imbalance has been regulated.

Reference is made to the work of L. R. Dragstedt at the University of Chicago, who showed that the parathyroids are intimately concerned with the neutralization of toxic wastes arising from the proteolytic action of bacteria in the bowel and that they are involved also in the neutralization of toxins arising from muscular activity. A. B. Luckhardt and his associates (*Proc. Soc. Exper. Biol. and Med.*, 1921, xix, p. 129; *Science*, July, 1922, lvi, p. 48) confirmed, in the same laboratory, the researches of Vines showing that the parathyroids are intimately concerned in the regulation of calcium

metabolism, and also with the subtle biochemical changes taking place during the menstrual periods and pregnancy. The theory has been advanced that these little glands are the regulators of the acid-base equilibrium of the body.

Then Hutton (*loc. cit.*, p. 180) tells of a number of clinical cases, one of which is especially interesting:

"Several years ago I saw a woman who had rhinitis, bronchitis, coryza, and whose maxillary sinuses were filled with mucus. The rhinologist to whom she was referred said that the sinuses were not the seat of ordinary inflammation, but that they acted as a sort of cistern, into which a large amount of mucus was poured. This condition persisted for many months and was unaffected by any measures recommended in text-books or by kind friends. Finally, a determination of her blood calcium showed it to be only 7 mg. per 100 cc. of blood. Calcium was promptly given, intravenously, with startling results.

"This condition, which had been immune to all previous efforts on our part, subsided so promptly as to be little short of marvelous. Subsequent colds in this patient have always been benefited by the administration of calcium. This has been given by mouth, except during the first cold. I usually give the lactate, in teaspoonful doses, three times a day."

Referring to the even more important underlying thyroid phase of these especially susceptible cases, Hutton continues:

"Hypothyroidism has long been known to be accompanied by congestion of the upper respiratory tract. These patients sometimes develop asthma-like attacks, which can be cured by the use of thyroid. This was probably the basis of the thyroid cure for asthma which was announced some years ago. I do not believe that any particular kind of cold would be recognized as being due to hypothyroidism. To discover this condition, the patient, and not his cold, should be examined. If the condition is discovered, it should be relieved by appropriate treatment. If a cold accompanies it, the cold will undoubtedly be relieved by such treatment."

There is something better for these common colds than thyroid alone. The thyro-adrenal supportive formula, Adreno-Spermin Co.,* has been used extensively in just such conditions. The depletion, asthenia, and atonicity seen in these patients deserve treatment as well as the commonly related phases of dyscrinism, which "will undoubtedly be relieved by such treatment"—if a thyro-adrenal insufficiency is associated with the cold or with the subtle predisposing factor that makes certain people susceptible.

A good routine in such cases is Sol. Adreno-Spermin Co., 1 cc. intramuscularly twice the first day, then once a day for the next three days. The standard oral formula should be used simultaneously, 2 tablets q.i.d. for the first two or three days, then 1, q.i.d. Several of the supplementary measures referred to in the Appendix improve the response to organotherapy.

48. CONVALESCENCE

REFERENCE HAS been made repeatedly in this book to the term "hypocrinism" (65), which is endocrine depletion and a most common disorder. Convalescence from any serious toxemia, infection, or disease is essentially a syndrome in which the endocrines are recuperating with the rest of the body. Consequently, the convalescent patient is an excellent subject for the indicated organotherapeutic support. In many instances he responds particularly well to the treatment because, in the majority of cases, the original difficulty is over and the patient already is on the road to recovery.

The management of convalescence manifestly must differ according to the nature of the illness that has preceded. If this was an acute infectious disease, the defensive mechanism of the organism has been strained more or less in the effort to establish immunity (68). If the convalescence follows a surgical operation or an accident or a shock to the nervous system, there are always certain special indications to be met, by observance of which the patient may convalesce more satisfactorily.

In many cases of convalescence, a symptom that is very trying to the patient is the sensation of hopeless weakness, of an inability to stand fatigue, physical or mental, that is actually humiliating in proportion to the patient's former activity. This feeling of exhaustion, usually associated with a lowered blood-pressure, is commonly referable to a depletion of the adrenal resources.

In our consideration of hypoadrenia (35), attention has been called to the facility with which the thyro-adrenal system is played out in influenza, and how effective its support is. The same fundamental principle applies in virtually every convalescent patient, except those recovering from hyperthyroidism (63), where a modification of this same idea is applicable.

Anemia is a customary concomitant of depleting conditions, for the hemopoietic system, equally with the endocrines, is subject to depleting influences. Great benefit follows a short course of hemopoietic liver therapy, for it is particularly fitted to meet the nutritional and resistance phases of convalescence because of its marked blood-building powers (40).

As a part of the routine treatment of convalescents, the following is suggested: Adreno-Spermin Co.,* 1 cc. intramuscularly every other day (for only five or ten days) with 1 tablet q.i.d.; and Heparnucleate,* two 4.5-Gm. tubes daily (one at breakfast and the other at supper) for a week, followed by one tube daily for two or three weeks longer. A gain of from 20 to 30 points in systolic tension, 10 pounds in weight, and 1,000,000 r.b.c. during this time is quite an ordinary result. Obviously these gains bring with them much subjective improvement.

49. DENTAL CARIES

The Teeth in Defective Children—Soft Teeth in Pregnancy.

THE METABOLISM of lime and the growth of the body having been shown to be under endocrine control, considerable attention is now being paid from this point of view to disorders involving the lime content of the body, including the teeth. Therefore, the far-flung influence of the endocrines is found even in dental caries.

THE TEETH IN DEFECTIVE CHILDREN—It is well known that certain endocrinopathies are almost routinely associated with caries, and many serious nutritional disorders include a feature that involves the teeth. Study a few hundred developmentally defective children and it will no longer be necessary to lend emphasis to the frequency with which dental caries and soft teeth are found in such cases. It should not be said that caries is a manifestation of dyscrinism, but it is undoubtedly true that dyscrinism is often accompanied by caries.

SOFT TEETH IN PREGNANCY—Not only in children, but also in adults during serious acute diseases and particularly during or after pregnancy, we find endocrine upsets followed by quite sudden changes in the resistance of the teeth. A case in point is that of a young woman who recently gave birth to a baby boy and is now having "all kinds of trouble with her teeth," which seem suddenly to have begun to decay and disintegrate. In this woman, the changes occurring during pregnancy precipitated a change in the nutrition of the teeth. Since both antepartum and postpartum dental caries are quite common, it is reasonable to presume that the dental changes are the result of endocrine changes.

Unfortunately, the only way to cure such a condition is to prevent it. If, during pregnancy, a special attempt is made to maintain the endocrine functions by suitable detoxicative and eliminative measures and by organotherapy where indicated, it may be of real prophylactic value.

Otherwise, it is very difficult to accomplish anything in these cases, for it seems very much like "locking the stable door after the horse has been stolen."

When confronted with a case of this kind, the only thing to do is to give the treatment that should have been applied earlier—remineralization plus calcium fixation by means of parathyroid therapy, while the dentist patches up the results. Calcium lactate, from 5 to 7½ gr., with 1 tablet of Para-Spleen Co.* three or four times a day for several months, is recommended.

50. DERMATOSES

Acne—Angioneurotic Edema—Eczema—Furunculosis—Ichthyosis—Pigmentary Changes—Leukoderma and Vitiligo — Psoriasis — Scleroderma — Urticaria—Summary.

THE NUTRITION, circulation, and physiology of the skin are peculiarly under the control of the glands of internal secretion. Several of the manifestations of thyroid disorder, early and advanced, are found in the skin (67). Boils, carbuncles, and gangrene commonly occur in connection with pancreatic diabetes (52). Chronic ulcers have been found to be related to the parathyroid functions (95). Then there are the dermatologic manifestations of allergy (36), which have undoubted endocrine connections.

P. L. Bosellini, of Rome (*Dermat. Wchnschr.*, Feb. 7, 1931, xcii, p. 210), emphasizes the extreme complexity of the problem in most dermatoses believed to be associated with endocrine dysfunction, except those with the classical symptoms of myxedema or Addison's disease, for example. After the dermatologist establishes his suspicion, he must remain in doubt as to which gland or glands are at fault; he has always to remember that the failure of one secretion may involve a partial or complete disorganization in the output of others. Even then his difficulties are not ended, for he has still to theorize on the nature of the dysfunction—whether it is temporary and functional, congenital and permanent, or brought about by some chronic inflammatory or malignant changes in the gland parenchyma.

Bruno Bloch, of Zurich (*Arch. Dermat. and Syph.*; Jan., 1929, xix, p. 22), discusses a series of skin diseases that he believes to have a direct endocrine origin. He calls them the dyshormonal dermatoses. These idiosyncratic dermatoses depend upon (1) exposure to an antigenic substance, and (2) the capacity of a given organ to produce specific antibodies. It is in this second factor that the personal and often constitutionally hereditary character of idiosyncrasy lies. Bloch affirms that it involves the vegetative nervous system and the endocrine glands.

W. T. Sack, of London (*Brit. Jour. Dermat. and Syph.*, Nov., 1928, xl, p. 441), suggests that many of the so-called allergic skin diseases, especially those with a background of mental or emotional irritation, are of endocrine interest. Recent conceptions indicate that the similarity of certain allergic conditions may be attributable to autonomic nervous alterations. Sack says:

"It is further an established truth that a correlation exists between the autonomic nervous system and the endocrines, and that malfunction of one cannot be present without disordered action of the other."

The moral is: Be sure to look for endocrine disorder and correct it if possible, as part of the routine treatment of all dermatoses.

We shall now consider several common dermatoses directly related to dyscrinism.

ACNE—Acne vulgaris, like other dermatoses, is a quite definite condition of known origin. A certain organism known as the *Bacillus acnes* is usually found to be the active agent. We are interested in acne especially because the susceptibility of these localized infections appears to be based on an endocrine foundation.

The youthful patient with acne too often is dismissed by the doctor with the admonition to "eat less sweets; it will disappear of itself in time anyway." It may be true that it will disappear "in time," but, to youth, that period is a long time of embarrassment and discomfort. Careful study of these cases often makes it possible to determine the underlying causes and leads to a far better control of the acne and the accompanying disturbances.

Contrary to the commonly accepted opinion, acne is not attributable to "too many sweets" and the dissipation of youth. It is a disease of the sebaceous glands, appearing usually at adolescence and disappearing spontaneously at the age of twenty-four or twenty-five. There is, no doubt, a dysfunctioning of the sebaceous glands or their ducts, as is seen in the clogging of the duct with inspissated material, followed by an inflammatory reaction around the duct or gland. But why is it that acne is most frequent at or near puberty? Again, why is it that acne in girls is frequently associated with or exaggerated by menstrual disorders? A study of the incidence of acne in a large number of girls indicates a definite connection between the ovarian function and whatever it is that permits the development of these localized infections—the resistance of the skin.

Now, we know that the thyroid gland has much to do with the nutrition and physiology of the skin, and, further, that patients with myxedema or ultimate degrees of hypothyroidism quite commonly suffer from dermatoses. Is it not possible, then, that the stress which the gonads place upon the thyroid and other intimately associated glands in connection with the outstanding endocrine developments of puberty, interferes with the capacity of these endocrines to regulate the nutrition and defenses of the skin?

The approach of puberty is characterized by certain familiar body changes and the development of the secondary sex characteristics. One of the first and most common manifestations in the skin is an increased oiliness or seborrhea, the face and the scalp being particularly affected. Seborrhea, it is admitted, is usually connected with puberty and is also a predisposing factor

in acne. Immunity to ordinary infective bacteria is often lowered during puberty. Acne almost invariably develops at the puberal period and, if untreated, terminates of itself within the period that the body requires to adjust itself to the introduction of the new endocrine factors.

Since these facts seem undoubtedly to involve the endocrines in acne, treatment is directed at the underlying conditions rather than at the disconcerting manifestations. The local and general treatment remain the same, and girls may be given Thyro-Ovarian Co.* with good prospects.

Unfortunately, what might be called corresponding treatment in young men is not so effective. Usually, gonad-stimulating therapy is contraindicated, but small doses of Endothyrin,* as little as ½ gr. a day, for several months may make a great deal of difference. Anterior pituitary, and sometimes adrenal substance, may be added as it is needed to establish a proper endocrine ratio. Iron and arsenic are given as may be indicated. In response we find that the boy ceases to blush so readily; he is less easily confused, and less self-conscious and bashful, all of which indicate that he is attaining a proper endocrine balance. And, simultaneously, in some cases the acne diminishes.

ANGIONEUROTIC EDEMA—The family of transient, neurocirculatory, irritated swellings of the skin and mucous membranes, including angioneurotic or Quincke's edema, erythema multiforme, urticaria, and a condition resembling purpura, is now believed to be caused by an allergic sympathetic reaction. The edema is most uncomfortable with its intolerable itching and burning sensation, but it is not dangerous. However, when the mucous membranes are attacked instead of the skin, acute digestive and alimentary symptoms may appear. The most alarming form of angioneurotic edema is that involving the larynx, for it may terminate fatally.

Adrenalin, from 5 to 10 minims of the 1:1000 solution, has been used with prompt results. Ephedrine (from 1/10 to 3/10 gr., t.i.d.) lessens the severity of the symptoms and shortens the attacks.

The solution of these problems is well under way. The relations of allergy and endocrine therapy (36) should be developed further, and an explanation sought for the relation between these dermatoses and eosinophilia. (See under "Urticaria" on page 373.)

ECZEMA—According to the statistics of one million cases compiled by Herman Goodman, of New York (*Arch. Dermat. and Syph.*, May, 1931, xxiii, p. 872), eczema and acne are the most common dermatoses. I quite agree with R. Friedman, of Philadelphia, who would discard the term "eczema" for "dermatitis." Eczema, he says, is to the skin as dyspepsia is

to the stomach—a vague term conveying no definite meaning. The many causative factors of eczema include disturbances of the alimentary, endocrine, and metabolic functions, such as gout, obesity, and hyperglycemia. The actual cause of the eruption is still obscure, and all treatment remains empirical.

While investigating the cause of eczema in infants, M. L. Ravitch and S. A. Steinberg, of New York (*Jour. Cutan. Dis.,* May, 1919, xxxvii, p. 313), were impressed by the frequency with which it occurred in breast-fed babies. These workers found that the largest percentage of cases were in children whose mothers showed thyroid disorder during either pregnancy or lactation. They believe that the milk of goitrous mothers is capable of causing a thyroid disturbance in the nursling. The thyroid is not able to maintain a normal metabolism, and the result is shown in the peculiar type of eczema found in the child. Iodides are recommended. If there is evidence of hypoactivity of the thyroid in the child or the mother, thyroid is given.

F. M. Pottenger, of Monrovia, California (*Endocrinology,* March-April, 1926, x, p. 105), has studied skin conditions particularly in the tuberculous. The skin is often dry and scaly; the hair tends to fall out and become gray; the pigment changes. Although these symptoms are usually ascribed to the fever, Pottenger believes that they are

"... representative of an altered function in the vegetative nervous system that controls these structures [skin and appendages]. Especially are some of these changes found in hypofunction of the thyroid gland.... These lesions do not represent pathological conditions of one phase of vegetative control to the exclusion of others, but rather a general disturbance in all: the nerves; the endocrine organs, particularly the thyroid; and the automaticity of the cell itself, particularly as it depends on its ionic condition, its permeability, and reactivity."

This author also believes that there is an hereditary factor in eczema. The relation of the vegetative nervous system is again considered, and it is shown that the functions of the skin are presided over by this system. The frequent relation of exacerbations to weather conditions suggests the connection between eczema and those factors that control metabolism; the disease is worse in cold weather when greater metabolic activity is required. The sympathetic nerves become more sensitive and the energizing glands of internal secretion, particularly the thyroid, more active.

In the treatment of eczema, particularly when associated with tuberculosis, Pottenger found that suitable doses of thyroid and calcium together kept the skin in better condition than thyroid alone.

Some interesting developments in the treatment of eczema and urticaria with spleen solution are considered further on page 374.

FURUNCULOSIS—Obviously a boil is not an endocrine disorder and should not be expected to respond to endocrine therapy, but two boils following in quick succession, then three or four or more, sometimes several together, are surely the result of a general defect that extends far below the skin.

Of course, a boil, being a collection of pus, should be brought to a head and evacuated as satisfactorily as possible. There is nothing that can be done for this from an endocrine standpoint. But, if we recall the interesting clinical fact that diabetics are peculiarly susceptible to boils and carbuncles and gangrene, it may lead us to some therapeutic possibilities that are not generally accepted.

As a matter of fact, in 1913, a paper of mine was published in the *Practitioner* (Aug., 1913, xci, p. 289), entitled "The Influence of the Pancreas and Extracts Thereof on Resistance to Infection," in which quite a little information was gathered to confirm the now generally accepted opinion that certain of the endocrines do, indeed, have to do with the susceptibility to infection. There is evidence to support the belief that phagocytosis is influenced by endocrine activities. In fact, Sir Almroth Wright once said that all the substances involved in immunity were of an endocrine nature.

Some years ago, an attempt was made to study a series of diabetic patients from the standpoint of their phagocytic activity, and in every one there was found a lowered resistance. As yet, there is little specific information available bearing upon this matter, but clinical experience confirms the suggestions of past years that suitable organotherapy directed at the pancreas also modifies resistance. Confirming this is some laboratory work done by a German author, A. Strubell, of Dresden (*Deutsch. med. Wchnschr.*, 1912, xlix, p. 2350), who shows that the administration of ordinary pancreatin increases the opsonic index to the staphylococcus. He adds that the extract of pancreas undoubtedly contains a substance that is concerned with the defenses of the body.

In this connection, Leonard Williams, of London (*Practitioner*, 1911, lxxxvii, p. 605), aptly remarks:

"It is time we set ourselves seriously to examine and appraise the side of the account which is presented by the cultivation of the normal process of resistance to bacterial invasion. . . . Not only are the defenses there, asking to be studied, but they afford a subject of inquiry as fascinating as any in the whole range of medicine, and as fruitful in promise as any in the whole range of therapeutics."

The essentially nutritional features of both acne and furunculosis are stressed by R. L. Sutton, of Kansas City. In an article in the *Archives of Dermatology and Syphilology* (Dec., 1928, xviii, p. 887), he reports a

number of experiences with liver therapy as a supplementary measure in particularly resistant and obstinate cases in these categories. He concludes:

"In certain chronic pustular disorders of the skin, and particularly in those in which there is an associated secondary anemia, the ingestion of liver extract may prove highly beneficial."

It must be added that hemopoietic liver therapy accomplishes more in a nutritional way than can be accounted for merely by the improvement in the blood-picture (40).

ICHTHYOSIS—Marie Krogh and C. With, of Copenhagen (*Ugesk. f. Læger,* May 17, 1923, lxxxv, p. 353), found in a large series of investigations that ichthyosis is often associated with a reduction in the basal metabolism. Since thyroid therapy specifically increases the basal rate, these Danish physicians treated a number of patients with thyroid, and "in several cases effected marked improvement in the ichthyosis." This clinical success confirmed the view of earlier writers who had connected hypothyroidism with ichthyosis. However, Krogh has not been able to establish any definite relationship between the severity of the ichthyosis and the extent of the change in the basal metabolic rate.

Later, it was reported by Arthur Porter, of London (*Brit. Jour. Dermat. and Syph.,* Dec., 1926, xxxviii, p. 576), that 70 per cent. of a large series of cases of ichthyosis among children and 25 per cent. among adults showed a subnormal B.M.R. This factor is the most certain indication whether or not the patient with ichthyosis is likely to benefit from thyroid. Porter adds:

"Treatment with thyroid extract should always be tried in ichthyosis, as 70 per cent. of children and 25 per cent. of adults have a subnormal basal metabolic rate.

"Ichthyosis in children is frequently accompanied by, and is possibly consequent upon, hyperthyroidism in the mother, although the theoretical connection is obscure.

"The reason for ichthyosis not appearing in a marked form so frequently until after weaning, is quite possibly due to the thyroid deficiency in the infant being compensated for by the mother through the milk.

"The degree of ichthyosis present in any given case is no guide to the basal metabolic rate in that patient. The most severe cases may have a normal or hypernormal basal metabolic rate."

PIGMENTARY CHANGES—Pigmentary changes may be engendered by disturbances of the pituitary, the adrenals, the thyroid, or the genital glands; and it may be stated broadly that a pluriglandular dysfunction may lead to either excessive or reduced pigmentation of the skin. In his interesting volume entitled "Glandes endocrines et dermatoses" (Paris, A.

Maloine et Fils, 1924, p. 163; reviewed in *Endocrine Survey,* April, 1925, ii, p. 160), A. Winstel says that several of the endocrine glands are able to modify the pigment of the skin in different ways, the color varying from the pasty condition of myxedema to the bronzing of Addison's disease.

Melanoderma—Until recently, brownish pigmentation (bronzing) of the skin was attributed chiefly to adrenal insufficiency. However, A. Sézary, of Paris (*Presse méd.,* April 9, 1921, xxix, p. 281), has shown that not every case of melanoderma is chargeable to this disorder, but that among the endocrine causes there may be hepatic, thyroid, or pituitary upsets.

Illustrative of these influences on the condition of the skin are the disturbances in pigmentation during certain periods when the endocrine system seems to be profoundly disturbed. At puberty the genital organs and the mammary areolas acquire a pigmentation that persists thereafter, but this phenomenon is not observed in subjects afflicted with infantilism caused by thyroid or pituitary insufficiency.

During pregnancy, which causes certain marked modifications in all the endocrine glands, there appears a characteristic expression that this French author calls "the mask of pregnancy," also the brownish line on the abdomen due to an excess of melanin in the epidermal cells. It is hardly necessary to mention hypertrichosis (64) with the appearance of hair on the chin and upper lip in women approaching the menopause.

As W. P. Graves, of Harvard University, says in his text-book ("Gynecology," Philadelphia, W. B. Saunders Co., 1929, p. 121):

"There is a close and well-known relationship between pigment hypertrophy and the functions of the pelvic organs at the time of puberty; there is a physiologic increase of pigment seen especially in the skin of the external genitals, about the nipples, and along the linea alba. During pregnancy the pigment of these areas is markedly hypertrophied, irregular spots of brown pigmentation appear on the face (chloasma gravidarum). Increase of pigmentation is often seen in individuals suffering from menstrual disturbances, chiefly amenorrhea and dysmenorrhea. With pelvic tumors, especially the large ovarian cysts, there is often a noticeable increase of pigmentation."

Chloasma, sometimes known as "liver spots," is a pigmentary skin discoloration due to conditions associated with pregnancy (*c. gravidarum*), cachexia (*c. cachecticorum*), and to constant exposure to the sun in the tropics —tropical mask (*c. bronzinum*).

There is nothing positive about the origin and nature of chloasma, but it is so like the bronzing of addisonism and is noted so often in conditions associated with adrenal insufficiency (the chloasma of consumptives, of cancer, of chronic malaria, etc.) that it has been associated with hypoadrenia.

Chloasma is more frequent in women, especially during pregnancy and at the menopause; in fact, there is a form of this disorder named *chloasma uterinum*. Chloasma of pregnancy is the name given to the sharply circumscribed irregular gray or grayish-bronze spots observed in pregnant women. These spots are usually symmetrical and are found on the forehead, on the alæ of the nose, around the eyes, and more rarely on the chin and cheeks. They persist after confinement until menstruation is reestablished, seldom longer.

The relation of chloasma to the internal secretions is suggested by the time of its appearance. For instance, chloasma occurs in the climacteric and in other disturbances of ovarian function such as dysmenorrhea, and in purulent inflammation of the adnexa. This fact suggests the significance of ovarian hypofunctioning.

The treatment of chloasma is the treatment of the dyscrinisms that may be related to it. If there is hypoadrenia, naturally it should be treated (35); if dysovarism is present, the indication is clear (80); and whenever there is liver stress—and undoubtedly there is a real basis for the old name, "liver spots"—hepato-biliary encouragement is always in order (104).

I have found that the control of chloasma is dependent upon the age of the patient; the prospects become less as the age increases.

LEUKODERMA AND VITILIGO—The peculiar condition of apigmentosis that is encountered from time to time is frequently reported in connection with dyscrinism. There are two names used to indicate this pigmentary dystrophy, "leukoderma" and "vitiligo." The former usually is considered to be congenital and the latter acquired.

While vitiligo may occur in a number of endocrinopathic pictures, such as dysovarism, pituitary disease, and even adrenal disease (despite the fact that this last almost always is related to the pigmentary antithesis), there are many more reports connecting hyperthyroidism and vitiligo. In their report of a case of vitiligo and Graves' disease in a young woman of twenty, C. I. Parhon and M. Dérévici, of Jassy, Roumania (*Rev. franç. d'endocrinol.*, Feb., 1929, vii, p. 12), express the belief that the vitiligo was due to the hyperthyroidism, because in some experimental research they succeeded in bleaching dark-colored feathers of birds by overdosing them with thyroid—which is interesting enough but of little clinical utility. As a matter of fact, there are no encouraging reports of any treatment, endocrine or otherwise, that will restore the missing pigment even though an associated dyscrinism may be treated effectively with the indicated organotherapy.

PSORIASIS—Since 1926, F. F. Ward, of New York City, and others have been using a thymus nucleoprotein solution in the treatment of psoriasis.

Empirical interest in this idea was stimulated some years ago by F. Samberger, a Vienna dermatologist (*Dermat. Wchnschr.*, 1918, lxvii, p. 687). At Ward's request, a non-irritating thymus solution known as Thymocrin* was perfected, which is given by intramuscular injection. In his paper in the *Medical Journal and Record* (Aug. 17, 1927, cxxvi, p. 216), Ward states:

"From actual experience, I am convinced that thymus solution . . . has a decidedly beneficial effect in the trophic disturbances of the skin of which psoriasis is as rich an example as we can find."

Later, in an item on the present-day treatment of psoriasis in the *Journal of the American Medical Association* (Feb. 18, 1928, xc, p. 564), the editor remarks:

"Endocrine therapy offers a promising field for investigation, particularly the rôle of the thymus gland."

There are a number of encouraging reports regarding the use of Thymocrin. In two groups of cases treated in a German hospital, the percentage of complete recoveries was claimed to be "at least 60." Five cases treated in Liverpool under the auspices of the Ministry of Pensions, and three cases treated in Guy's Hospital, London, are reported to have been cleared up entirely.

Many physicians have used this product, and, while the reports vary, there are many who claim that it has been most helpful. But the reason for this benefit is not yet apparent. Some have thought that it might be due to a non-specific protein influence; but there is practically never a local or general reaction. Others, recalling the fact that the thymus was the original source of nuclein, have thought that it might act as a leukocytogenetic like sodium nucleate, but it does not. The question is still an open one.

It is hard to find acceptable explanations of an endocrine basis of psoriasis. R. Carillon, of Nancy, France (*Rev. franç. d'endocrinol.*, Feb., 1926, iv, p. 32), suggests that there is a psoriatic heredity in which endocrine alterations —not always in the same gland—bring about disturbances in the tonus of the vegetative nervous system, acting directly through the sympathetic. According to this author, these changes cause the sympathetic system to lose its normal control of the nutritive exchanges, and there is a consequent impairment of the epidermal metabolism. But this does not explain the matter very well. Carillon adds that the treatment of psoriasis must affect both the occasional and the underlying cause, the former by external measures and the latter by rectifying the sympathetic tonus. He has found thymus extract and insulin more effective for this purpose than any other endocrine product.

With regard to thymus in psoriasis, the editor of the *Prescriber* (Oct., 1929, xxiii, p. 363) has this personal comment to make:

"In our review two years ago (PRESCRIBER, Nov., 1927, xxi, p. 409), mention was made of the successful treatment of some cases by intramuscular injection of an extract of thymus gland ('thymocrin'). No explanation was offered, and one might be excused for being skeptical. Since then, however, thymocrin has been tried in this country in a number of cases, and reports received privately by the present writer indicate that considerably more than half these cases already have definitely cleared up. Whether or not recurrences will take place, it is, of course, impossible to say; but even temporary relief is welcome. The average course of treatment is from sixty to eighty intramuscular injections of 1 cc., five injections being given weekly. Generally there is little improvement, if any, during the first three weeks; and some cases, it must be stated, give no response whatever."

According to Ward, it is preferable to give an intramuscular injection of 1 cc. of Thymocrin* every day for a month, if possible, otherwise every other day. So far this preparation has been credited with causing a total disappearance of the lesions in a sufficient number of cases of psoriasis to make it worth a trial, although some types do not respond at all.

SCLERODERMA—Several of the peculiarities of this affection remind one of the thickened, dry, rough skin of ultimate degrees of hypothyroidism. Yet there is a difference between the myxedematous skin and scleroderma. The present opinion regarding the origin of this condition connects it with abnormal function of the neuro-endocrine mechanism, which idea is confirmed by the frequency with which dyscrinism accompanies scleroderma.

Gustav Singer, of Vienna (*Med. Jour. and Rec.*, March 17, 1926, cxxiii, p. 374), made a series of anatomical studies, as a result of which he definitely connects the origin of scleroderma with thyroid dysfunction. He claims to have been the first to recommend thyroid in the treatment of this malady. Many others have followed suit with advantage. Singer says:

"Scleroderma is not always of purely thyrogenic nature, and examples of pluriglandular functional disturbances are well known. The combination of loss of ovarian function and disturbance of the thyroid gland is not rare, and, according to my experiences, the combined treatment with corresponding organic preparations often shows surprising results."

URTICARIA—The treatment of urticaria, eczema, and other allied types of dermatitis with massive doses of spleen solution constitutes an advance into the biochemical unknown. The clinical developments are very interesting, and bid fair to revolutionize some of our conceptions of the whole subject.

Basing his work largely on the conclusions of the Swiss school, L. von Zumbusch, of Munich (see *Urol. and Cutan. Rev.*, Dec., 1927, xxx, p. 750), reports some researches on the spleen. Mayr and Moncorps, two of his pupils, showed that experimental splenectomy in laboratory animals causes a marked eosinophilia and that the curve of the eosinophilic cells runs exactly as it does in anaphylaxis. They concluded that either the spleen hems in the eosinophiles, or that anaphylaxis, accompanied by eosinophilia, is produced by defective spleen function.

At first Mayr and Moncorps used stimulating doses of X-ray to the spleen, but, because of the frequent injuries resulting from this, they tried organotherapy. They found that even a very small injection of an albumin-free spleen extract diminished the number of eosinophiles and stopped the itching. Similar results were obtained in other dermatoses associated with eosinophilia. A case of long-standing, generalized, desquamative erythrodermia was cured. Eczemas in patients with an exudative diathesis were promptly ameliorated. Although the initial relief is only temporary, continued spleen injections frequently make the effect permanent. Von Zumbusch mentions cases of eczema of ten years' standing, that were entirely cured by the spleen therapy after every other treatment had failed. Numerous cases of bronchial asthma also have been benefited.

R. Birke, of Munich (*München. med. Wchnschr.*, Nov. 23, 1928, lxxv, p. 2009), gives a comprehensive report of eighty cases of various dermatoses with careful studies of the eosinophile counts and variations. It is stated that an eosinophilia exceeding 8 per cent. is considered an indication for spleen therapy. Counts made at intervals of one and two hours showed that the fall in eosinophiles reaches its lowest figure between six and eight hours after the injection. The response in the dermatosis parallels this, although, according to Birke, the response to the first injection is less than to subsequent ones, and the benefit is more prolonged with each new injection.

The summary of the results in these eighty cases gives a fall in the eosinophiles in all of them, simultaneous abatement of itching in 80 per cent., and definite improvement in the dermatoses in 65 per cent. Birke states that the good results were especially marked in chronic eczema dating back to childhood, as well as in those dermatoses associated with asthma.

Thomas Paul, of St. Joseph, Missouri, has treated many dermatoses with this new method. He begins an article (*Urol. and Cutan. Rev.*, Nov., 1929, xxxiii, p. 724) with this startling statement:

"To state that hives will disappear in fifteen minutes, that itching and oozing of eczema will cease in half an hour, and that an eczematous lesion,

regardless of its degree of lichenification, will vanish in a few days as a result of hypodermic injection, seems preposterous, yet such has been the writer's experience in a series of sixty-one cases."

Beginning with 1-cc. injections of spleen solution, Paul gradually increased the dosage to 12 cc. at one injection.

Since the earlier watery spleen extracts contained too much protein to permit of their use in doses of 12 to 15 cc., a special deproteinized concentrate known as Splenocrin* was made in order to make von Zumbusch's idea available in this country. For two years a number of physicians have been using it in graduated doses of from 2 to 20 cc., intramuscularly, for the treatment of eczema, urticaria, and conditions of protein sensitization including asthma and hay-fever where there was also an increase in the eosinophiles.

Splenocrin contains only 37 mg. of solids in each cubic centimeter; nevertheless, it is advisable to give an initial injection of 2 cc. to test the patient's sensitiveness; then on the next day inject from 5 to 10 cc., depending somewhat upon the patient's weight. Two days later give another intragluteal dose of 15 or 20 cc. One large injection often suffices, although several may be given at intervals of two or three days. It is evidently advantageous to reduce the dosage gradually.

P. Chevallier and L. Bloch, of Paris (*Bull. et mém. Soc. méd. d. hôp. de Paris,* Dec. 22, 1930, liv, p. 1814), report several cases that demonstrate the excellent results they have secured during the last year by using aqueous splenic extract in the treatment of pruritus and eczema. Each cubic centimeter of their extract represents 12.5 Gm. of fresh veal spleen. At first they injected 2 cc. every other day, later doubling this dose. The larger doses sometimes cause a slight fever and general feeling of discomfort, undoubtedly a protein reaction due to the product's not being deproteinized sufficiently. The fact that neither diet nor local cutaneous treatment is necessary, makes these authors feel that spleen therapy is an important therapeutic development.

The benefit that has been claimed for the use of spleen therapy must be of a general nature, because the preparation is injected intramuscularly and exerts a wide-spread influence. The reports testify to its efficiency and researches show that it also has a marked, though fleeting, effect on the blood calcium.

Some further explanations regarding this remarkable development are offered in the consideration of the various preparations obtained from the spleen (21).

Non-specific protein therapy (105) has been used extensively in dermatologic practice, and, since it is believed to produce an essentially endocrine response, it is considered as a form of indirect endocrine therapy.

C. S. Wright, of Philadelphia (*Arch. Dermat. and Syph.*, Jan., 1931, xxiii, p. 118), asserts that non-specific therapy is of definite value in the treatment of a number of diseases of the skin. Autohemotherapy may prove of distinct benefit in the treatment of psoriasis, as an adjunct to local therapy and in lessening the activity of the eruption; it is often a great aid in the treatment of patients with chronic urticaria. Milk preparations are of value for the immediate treatment of furunculosis and carbunculosis. Pruritus of idiopathic origin or severe pruritus accompanying a dermatosis may in some instances be relieved quickly and effectively by the intramuscular injection of a milk protein. In eczema, acne, and psoriasis, milk preparations have proved disappointing. Non-specific vaccine therapy with a *S. fæcalis-B. coli* vaccine is claimed to have been of some value in the treatment of several cases of psoriasis.

SUMMARY—As a suitable summary to this collation of data, I shall submit the conclusions made by Moses Scholtz, the Los Angeles dermatologist, in his excellent article "Endocrinotherapy in Skin Diseases" (*New York Med. Jour.*, July 6, 1921, cxiv, p. 68), published just ten years ago as I write. His conclusions are still as reasonable and fair a statement of the subject as one can find:

"1. Endocrinotherapy can be accepted as the method scientifically valid and clinically effective.

"2. Hypothyroid dermatoses are the most definitely established and therapeutically successful group.

"3. To the hypothyroid group can be assigned, apparently, the following dermatoses: (a) various forms of dyskeratosis: ichthyosis, congenital keratodermias, Darier's kerosis, lichen pilaris, Darier's keratosis follicularis; (b) certain dry, squamous eczemas and certain cases of psoriasis, Hebra's prurigo, senile pruritus and hypothyroid pruritus, possibly scleroderma.

"4. Indirectly and non-specifically various hormones are beneficial in various symptomatic dermatoses, such as acne vulgaris, rosacea, dietetic and vasomotor dermatoses, and diabetic eczemas.

"5. The substitution principle of endocrinotherapy, *i.e.*, the supply of deficient or absent hormones, at present is the most productive and clinically most applicable.

"6. The best results are obtained by the administration of small doses for a prolonged period of time."

51. DIABETES INSIPIDUS

Chronic Polyuria—Post-Pituitary Therapy—Intranasal Applications.

CHRONIC POLYURIA with a correspondingly intense thirst, or polydipsia, is a rare condition that is now believed to be caused by a lesion in the infundibular stalk, or pars intermedia, of the pituitary gland.

Diabetes insipidus is a poor name for this disorder, for it is quite unlike diabetes mellitus, the clinical differences being in the character of the urine and the lack of certain other symptoms. The urine in true diabetes is of high gravity with excessive solids, consisting chiefly of sugar; in diabetes insipidus, the amount of urine is even larger (10 liters or more a day), but the specific gravity is from 1.002 to 1.005, and the total twenty-four-hour solids is approximately normal.

There seems to be a neurotic basis for this disease. For instance, it may follow an emotional upset or a cranial injury. Also it has been found associated with tertiary syphilis in which nerve involvement was present. Antisyphilitic therapy has coincidentally controlled the polyuria in certain of these cases.

POST-PITUITARY THERAPY—The present-day treatment of diabetes insipidus is purely empirical, though quite effective. Nearly twenty years ago, F. Francisco, of Milan (*Gaz. d. osp.*, 1913, xxxiv, p. 1127), found that an injection of a comparatively small amount of pituitrin once or twice a day caused spectacular changes in the thirst and polyuria, with corresponding comfort to the patient. His position was confirmed later by L. F. Barker and M. Hodge, of Baltimore (*Endocrinology*, Oct.-Dec., 1917, i, p. 427), who expressed the opinion that diabetes insipidus is due to insufficiency of the pars posterior of the pituitary. They found that injections of infundibulin promptly arrest the symptoms, though this benefit often varies very widely.

It has been shown more recently that the antidiuretic action of pituitary extract is due to its pressor principle, vasopressin, and the employment of this fraction of pituitrin is now being recommended in the treatment of diabetes insipidus.

The study of the extent of the pituitary damage or, perhaps, the balance that regulates water excretion is made possible by a therapeutic test. This test (31) consists in having the patient drink a quart of water two successive mornings, on the second of which an injection of pituitrin is given. The amount of urine passed during several hours after the injection, is measured and compared with that of the day before.

The treatment of diabetes insipidus is symptomatic. Injections of graduated amounts of pituitrin are given daily or more frequently until the optimum dosage is discovered, which usually ranges from 10 to 20 international units a day. This dosage is continued more or less indefinitely, for it affords only temporary relief.

INTRANASAL APPLICATIONS—More recently attempts have been made to avoid the innumerable injections. Thus a method of application by way of the nasal mucosa, originally suggested by Harvey Cushing, of Boston, was first tried by H. L. Blumgart (*Arch. Int. Med.*, April, 1922, xxix, p. 508) in 1922. John R. Campbell and H. L. Blumgart, of Boston (*Am. Jour. Med. Sc.*, Dec., 1928, clxxvi, p. 769), report on eight cases in which the polyuria and polydipsia were effectively checked by this treatment. Two methods are suggested: In one, pituitary extract (the obstetrical, or weaker strength) is sprayed into the nasal cavity in quantities varying from 0.5 to 1 cc. every three, four, or six hours, so as to be deposited mostly on the roof of the nasopharynx. The second method, which is preferred, consists in the application of from 0.5 to 1 cc. of the liquid by means of a cotton swab, which is passed high up into the nasopharynx—an important point—and left in situ until the next application. Occasionally a burning sensation is produced, but this usually passes off, though in one case treatment had to be discontinued on account of it.

A. R. Kintner and C. H. Greene, of the Mayo Clinic (*Jour. Am. Med. Assn.*, Nov. 3, 1928, xci, p. 1370), regard the nasal spray as next in effectiveness to the injections, while it is free from the obvious inconveniences of hypodermics. They use "the purified pituitary extract described by Kamm" (vasopressin?) in doses of 1 cc., which is applied by means of a specially adapted glass atomizer that holds the necessarily small quantity of solution.

In France, Choay recommends insufflations of pituitary snuff, each dose being divided equally between the two nostrils, and the patient being careful not to blow the nose or sneeze for some time afterwards. In mild cases passing less than 10 liters of urine daily, from 5 to 10 cg. of powder a day, divided into two or three doses, is sufficient. For patients discharging from 15 to 20 liters daily, the dose should be 4 cg. three times during the day and from 6 to 8 cg. at bedtime. In the case of patients in whom the polyuria exceeds 20 liters, mixed treatment is necessary; an injection should be given either in the morning or at night, and the powder used during the day. The only contraindication being a pathological condition of the nose, a preliminary anterior rhinoscopy should always be made before starting treatment.

52. DIABETES MELLITUS

Our Conception of Diabetes Is Too Limited — A Broad Endocrine Dysfunction—The Adrenal-Pancreas Balance—An Hepatic Factor—The Relations of Secretin — Insulin in Diabetes — Pancreatic Support — Oral Pancreas Therapy—Diabetes in Children—Diabetic Gangrene—Summary.

UNQUENCHABLE THIRST; frequent micturition; gallons of urine; extreme loss of weight; marked weakness and susceptibility to infections, especially of the skin—these are the outstanding symptoms of diabetes mellitus. The diagnosis is confirmed by the findings of the urinalysis—high specific gravity, glycosuria, and acetone bodies—or by the blood chemistry.

The laboratory has demonstrated the facts upon which our present conception of diabetes is based, the clinical laboratory showing the carbohydrate intolerance and the extent of its control, and the experimental laboratory proving conclusively where the seat of the trouble lies—in the pancreas.

In 1877 the first suggestion of a relationship between the pancreas and diabetes was made by E. Lancereaux, of Paris. Then, for more than ten years, the matter lay in abeyance until almost simultaneously, in 1889, J. von Mering and O. Minkowski, in Germany, and R. Lépine, of Lyons, France, produced experimental diabetes by removal of the pancreas, thus unequivocally connecting the pancreas with diabetes.

The credit must be given to R. Lépine for having offered "a new theory of diabetes" and for using the term "pancreatic internal secretion." From that time until insulin was perfected in 1921, thousands of experiments have been performed and papers by the hundred have been published—some of them suggestive, others absurd, and all of them serving gradually to build a structure that now represents one of the greatest of the monuments to endocrine research.

For forty years the profession knew that the pancreas was involved in diabetes mellitus; for twenty years the conception of the pancreatic hypocrinism has been developed; and for almost ten years we have had insulin, the Langerhansian hormone, as a spectacular means of controlling the symptoms of diabetes. Yet, despite these magnificent attainments, according to Ralph H. Major, of Kansas City ("Eight Years of Insulin," *Jour. Kansas Med. Soc.*, Feb., 1931, xxxii, p. 42), the death-rate of diabetes mellitus is higher than ever.

What are the reasons? Have we overestimated the value of insulin? Are we getting all the advantage from Banting's materialization of Lancereaux's forty-year-old hints? Is there not something more we can do? The answers

to these questions will have to suffice for the basis of this brief consideration of diabetes mellitus, for the sum total of the contributions on insulin alone would exceed the contents of this entire book.

OUR CONCEPTION OF DIABETES IS TOO LIMITED—First of all, the conception of diabetes is still too limited. The patient has hypopancreatism, or hypoinsulinism as some call it, with a resultant carbohydrate intolerance that calls for two outstanding therapeutic measures: (1) the sparing of the pancreas by dietetic regulation, and (2) the replacement of the missing hormone. Each procedure leads to prompt symptomatic results—used together, the symptoms of diabetes are controlled most satisfactorily. The laboratory protocols are most encouraging, and the clinical statistics most convincing. Yet the vital statistics are giving us pause!

Secondly, the brilliancy of the accomplishments made possible by insulin has dazzled us. Its effects are so spectacular that we are satisfied, for are we not getting real results, and enabling our patients to eat more, gain in weight, and overcome the symptomatic discomforts already enumerated? Yes, indeed; but—.

Thirdly, we have fallen short in many of our diagnoses, for a diagnosis of diabetes is not enough. A diagnosis of "diabetes mellitus" is comparable with a diagnosis of "pneumonia." Such a diagnosis would have been acceptable twenty years ago, but to-day we need to know the location of the pneumonia, the numerical type of the infecting organisms, the complications, and the resilience of the vital mechanisms especially stressed in pneumonia—a far broader diagnosis than was once perfectly proper. Even so, our diagnosis of diabetes mellitus must now be qualified and extended, and as we are capable of doing this it is likely that there will be improvement in the vital statistics of diabetes mellitus just as there has been a most encouraging improvement in the statistics of pneumonia.

The consideration of these three premises may lead to a broader conception of the diabetes problem, and to a point of view that will cause us to expand the study and treatment of the disease.

A BROAD ENDOCRINE DYSFUNCTION—The cause of diabetes indicates to a certain extent its treatment and prognosis. Is it merely a pancreatic disease or does it involve other structures? If it does, what are these other organs and which are involved first?

The broader aspects of the etiology of diabetes have been emphasized for years. Twenty years ago, O. Minkowski, then of Alexoten, Russia (*Med. Klin.*, 1911, vii, p. 38), stated:

"Whenever a disturbance of a very definite order occurs, such as that in diabetes mellitus, there is every reason to seek for a localization of this disturbance. But one must not forget the following: Localization does not mean that the whole pancreas is limited to the bounds of a single organ. No organ works for itself alone. It depends on processes taking place in other organs, and the products of its own activity influence the functions of other organs. These products may be ferments which promote decompositions in the blood or they may be hormones which regulate the activity of cells. Functional disturbances in a certain organ may, therefore, affect other portions of the body. . . . The injuries may not be confined to damage to a single organ. They may, perhaps, especially influence a certain organ, but the diseased condition may also be the result of the most variable combination of local influences."

Several premises, which are partly clinical deductions and partly pure speculations, suggest that diabetes is (1) an upset of the sympathetic balance based upon a syndrome involving the emotions. If this is so, our treatment must take it into consideration, and this phase of the etiology must be controlled, else it will continue to militate against the success of any treatment we may be able to offer. Unfortunately, it is as hard to change a person's emotional stability as it is to teach the proverbial new tricks to old dogs.

Again (2), there is often a serious digestive stress which for years has imposed upon the entire alimentary mechanism, particularly the liver function. The liver barrier has been broken down, allowing many added duties to fall upon other organs, which they can ill afford to bear (66). The dietetic control helps this, of course, and so does elimination, but it is negative treatment, *i.e.*, it merely prevents further defects, leaving the accumulated functional and pathological limitations still to be controlled.

Finally (3), diabetes certainly may be built upon an infective basis—infection by contiguity from the duodenum or the gall-bladder and ducts, or a blood-borne infection. Without a doubt, a subacute pancreatitis complicates many a case of diabetes. To make our task more difficult, all these factors—(1), (2), and (3)—may be present in a greater or less degree. No wonder insulin and diet show their ultimate shortcomings.

THE ADRENAL-PANCREAS BALANCE—Since the pancreas is an integral part of the endocrine system, it must be influenced by other glands, just as it must influence them. Years ago the famous Carl von Noorden, of Frankfurt a.M., called the pancreas "a brake to the sugar factory," and showed that there is a nice balance between the pancreas and the adrenals. G. Zuelzer, of Berlin (*Ztschr. f. exper. Path. u. Therap.*, 1908, v, p. 307), was among the first to discover the fact that adrenalin glycosuria could be

suppressed by injections of an albumose-free pancreatic extract. The same year the Italian investigator, C. Frugoni (*Gazz. med. ital.*, 1908, lix, p. 372), confirmed this by showing that pancreas extract had the power to destroy adrenalin in vitro. D. G. Ghedini (*Gazz. d. osp.*, 1908, xxix, p. 1669), and later other investigators, showed that a fatal dose of adrenalin, when mixed with pancreas extract, is practically innocuous.

Since then several clinical confirmations have established the vital nature of this balance, upon which Loewi's test (31) is based. Walter B. Cannon's work at Harvard proved that stress so stimulates the adrenal medulla that the adrenal-pancreas balance is upset. Even such a temporary factor as the urge of a football game caused almost half the men in the Harvard football squad to have glycosuria after a game with Yale! (See "Bodily Changes in Pain, Hunger, Fear, and Rage," New York, D. Appleton and Company, 1915, p. 75.) Then, too, it has been shown repeatedly that the small amounts of adrenalin used in minor surgery frequently cause marked, though temporary, increases in the sugar index of diabetic patients.

Hence, the thoroughgoing control of pancreatic insufficiency must include also an appreciation and control of factors interfering with the adrenal functions.

AN HEPATIC FACTOR—The suggestion already has been made that the liver may be a vital factor in the diabetic picture and hypohepatism (66), or defective hepatic detoxication, a contributing feature to the complex nutritional upset. This idea is receiving increasing confirmation. For instance, clinical and laboratory studies made by E. L. Meyer, of Philadelphia (*Arch. Int. Med.*, Feb., 1931, xlvii, p. 182), on one hundred diabetics indicate that hepatic dysfunction is a frequent occurrence in diabetes mellitus. Of the cases studied, 7 per cent. showed both clinical and laboratory evidence of hepatic dysfunction, 28 per cent. furnished only laboratory data, 48 per cent. were without any abnormal indications, and 13 per cent. gave only minimal or doubtful readings. The older the patient and the longer the diabetes mellitus remains uncontrolled, the more frequently hepatic dysfunction becomes demonstrable. The study of these cases over an extended period of time created the impression that the modern diabetic regimen aids materially in improving the hepatic function.

Since the perfection of the hepatic detoxicative hormone (13), many a physician, noting its effect upon hypertension of the functional type (45) and the subjective improvement and euphoria that follow a comparatively short course of treatment with this hormone, has wondered why such enhancement of hepatic detoxication should not be extended to many other

toxemias when it is obvious that the accepted measures are falling short and it becomes necessary to broaden the treatment.

The addition of Anabolin* to other treatment of diabetes has caused symptomatic benefit. It is by no means a remedy for diabetes—there is no single remedy for diabetes—but, in suitable cases, it is a means toward one of the ends that it is necessary to reach in the treatment of the diabetic patient.

THE RELATIONS OF SECRETIN—The work of E. H. Starling, at University College, London (1902), showed how secretin influences the pancreatic digestive secretion (10). It was later (1905) proved by G. Pochon, of Paris, that secretin also affects the pancreatic endocrine secretion and, further, that secretin therapy adds to our ability to overcome the dyscrinism in diabetes. This part of the diabetic picture is too often neglected, save by the indirect method of dietetics. Why should our treatment be limited to one end (the tail) of the pancreas, when the gland as a whole has been stressed for years?

The whole hormone theory is based upon the experimental work with secretin, for, as we have seen (page 87), secretin was "the original hormone." I feel that one of the shortcomings in our consideration of diabetes mellitus concerns the pancreatic *acinous* function and the duodeno-pancreatic relationship.

In an earlier book ("Practical Hormone Therapy," London, Baillière, Tindall & Cox, 1914), I collected several reports of success from the clinical and experimental use of secretin in diabetes. I might mention, for instance, the first communication on the subject by B. Moore, E. S. Edie, and J. H. Abram, of Liverpool (*Biochem. Jour.*, 1906, i, p. 28), in which the oral administration of an acid extract of duodenal scrapings caused clinical improvement in diabetes mellitus; also the experimental work of F. A. Bainbridge and A. P. Beddard, at Guy's Hospital (*Guy's Hosp. Rep.*, 1907, lxi, p. 161), who showed that in many diabetics prosecretin is absent from the duodenum, *i.e.*, the makings of secretin are deficient, hence the difficulty in completing the cycle of secretin production and pancreatic activation (10). An interesting side play occurred soon after this. At University College, London, C. L. Evans (*Jour. Physiol.*, 1912, xliv, p. 461) made a series of experiments to ascertain the fate of prosecretin in depancreatized dogs. The information thus gained shows that total extirpation of the pancreas is rapidly followed by complete disappearance of the precursor of secretin in the duodenal walls; but, if a small portion of the pancreas is left (to preserve a sufficient amount of the pancreatic hormone for the prevention of glycosuria), there is no appreciable diminution in prosecretin. It is suggested that the loss

of secretin in pancreatic diabetes is simply one symptom in the general train of metabolic disturbances consequent on loss of the internal secretion of the pancreas. All of this should stress the more definitely digestive phases of diabetes and lead to a consideration of secretin as another weapon with which to attack the diabetic problem.

INSULIN IN DIABETES—Banting and Best's isolation of insulin in 1921 thrilled the discouraged diabetic world and removed a great burden from the shoulders of the profession. Insulin, originally made available as Iletin (Lilly), is an aqueous solution containing the antidiabetic principle obtained from the pancreas of animals. When injected subcutaneously, it enables the diabetic patient to utilize carbohydrates and fats in a virtually normal manner. Although insulin is not a cure, it replaces something that is missing in the body, thereby restoring weight and physical and mental strength, and making it much easier for the patient to carry on his usual work. Those who faithfully adhere to insulin treatment profit greatly, but those who are negligent die as a result of their carelessness.

One great advantage of this attainment had to do with the standardization of insulin. The original physiological unit of potency adopted by J. J. R. Macleod and his associates at Toronto University was the amount of insulin which, when injected subcutaneously into rabbits weighing 2 kg., lowered the blood sugar below 0.045 per cent. and produced convulsions within from two to five hours. This unit was considered too large for clinical purposes, so a provisional clinical unit was adopted which was one-third of this amount. One unit of insulin is therefore defined as one-third the minimum amount of the extract which, on subcutaneous injection into starved 2-kg. rabbits, will lower the blood sugar to the convulsive level (0.045 per cent.) within from two to five hours.

Insulin is administered subcutaneously; given orally, it is of no immediate value. It should not be injected intramuscularly nor too near the surface of the skin. Injections should not be made repeatedly into the same area, as induration may result and absorption of subsequent injections be hindered. The dosage varies, being determined by the patient's response—the blood-sugar curve. It is given one, two, or three times daily in definite relation to the meals. This is of peculiar importance. Insulin is generally given from a quarter to a half hour before meals, but some patients may do better with a different time interval. The lowering of the blood sugar often is evident within half an hour, and its effect is demonstrable for at least six hours and in some cases for ten hours or longer.

In most clinics the first step before commencing treatment with insulin is to learn the patient's glucose tolerance either by completely freeing the urine of sugar or by estimating the average daily excretion on a known and constant glucose intake. If the patient becomes sugar-free on the selected diet, the number of calories in the diet is increased gradually by repeated additions of small amounts of carbohydrates and fats until a working diet is attained or sugar appears in the urine. When a patient continues to excrete sugar after several days on the original test diet, or on any succeeding diet, up to that required to maintain him in health and normal activity, and when the daily excretion of sugar is fairly constant, insulin treatment may be started, the initial dosage being based on this information.

There are two procedures that may be followed: (1) Give 1 or 2 units of insulin three times a day, half an hour before meals, gradually increasing the dose if necessary until the urine is sugar-free. (2) Inject one unit of insulin daily for each 1.5 to 3 Gm. of glucose excreted (based upon the average amount excreted during the two or three preceding days), the dose being divided into two or three injections during the day according to the number of units required. If sugar continues to be excreted in significant quantities after the second or third day of insulin administration, the dose is gradually increased until the urine becomes sugar-free or nearly so. The use of a high initial unitage is to be recommended only when the patient is being observed closely and repeated blood and urine sugar determinations are made, in order to avoid the production of hypoglycemia—*i.e.*, the lowering of the blood sugar below the normal level (100 mg. per 100 cc., or 0.1 per cent.).

There are two dangers connected with the use of insulin: The patient may stop taking it without correspondingly decreasing his diet, which causes the diabetes to return and the diabetic to develop acidosis and coma. The other danger, which is known as the insulin reaction or hypoglycemia—"the shakes"—is caused by an overdose of insulin, and may also be fatal. All physicians are familiar with these symptoms, which may be miraculously overcome by immediately eating two teaspoonfuls of sugar or an orange.

To-day it is possible to obtain insulin anywhere. A unit can be bought for a cent or two, and, since the average patient uses between 10 and 20 units a day, the cost is now a minor factor. Many diabetics now treat themselves with insulin or receive it at home under supervision of varying degree, despite a natural reticence on the part of the profession to permit it. There is little difficulty in giving the hypodermics, though a new neurosis known as "needle horror" has been developed. There is available a large and

practical literature to guide these patients with their diet and treatment. (See Chapter 110.)

When we remember that there are probably a million diabetics in the United States, it is realized how greatly we are indebted to the discoverers of insulin who have made it possible for these unfortunates to live healthier and happier lives, even though we cannot yet predict if or when it will be possible eventually to cure the disease.

PANCREATIC SUPPORT—Knowing that pancreatic stress is a prominent cause of diabetes mellitus, and that the digestive as well as the endocrine mechanism is played out in most cases, it has seemed to me for twenty years—long before the advent of insulin—that something ought to be done to support the pancreas. Diabetes mellitus is the result of pancreatic damage, which may be functional or organic. In many of the functional cases it is entirely possible to reestablish the activity of the remaining sound Langerhansian cells. This does not mean that the pancreatic endocrine service is replaced (as is so effectively accomplished with insulin), but that the pancreatic functions (plural) are reestablished by homostimulative catalytic influences just as we expect depleted functions in other played-out glands to be restored by suitable endocrine interference.

There are two ways to attempt this: one directed at the endocrine phase of the difficulty, with a concentrate from the tail of the pancreas (15)—*not* pancreatin; and the other at the digestive phase, with an acid extract of the duodenum containing secretin (10). These two substances are combined in the formula, Pan-Secretin Co.,* which is given by mouth as part of the treatment of functional diabetes. It is of little or no value in Langerhansian atrophy and diabetes in children, an unfortunate fact which, however, adds to the conviction that the remedy is not active of itself but only as a result of the response that it is able to arouse on the part of the depleted pancreas.

Of course, this is but a part of the treatment of diabetes. Insulin is given for its immediate effects to prevent the sequence of events that lead to ketosis and coma, and to enable the body to utilize carbohydrate. Insulin also rests, or spares, the pancreas. Alkalies are given to overcome acidosis (100) and at the same time to save the whole endocrine mechanism, for the toxemia of diabetes exerts a wide-spread detrimental effect on the endocrine system as a whole. Diet is just as necessary a part of this treatment as it is when insulin is given alone. The pancreatic support is simply an attempt to utilize two known endocrine catalysts, and its success or failure depends entirely upon the capacity of the pancreatic cells, both acinous and endocrine, to respond to these influences.

The results are not so rapid nor so spectacular as those from insulin. Insulin does the work for the body at once, of itself. Pancreatic support is helpful only as the pancreas can and does respond to these stimuli. It takes time. Herein lies another great endocrine misunderstanding to which it is essential that attention be called.

ORAL PANCREAS THERAPY—There is still a wide difference of opinion regarding the availability of pancreas therapy by mouth. A recent, concise expression of opposition is found in the *Journal of the American Medical Association* (Jan. 10, 1931, xcvi, p. 134):

"That pancreas preparations taken by mouth are not efficacious in the treatment of diabetes mellitus is the overwhelming consensus of all eminent students of this question. It is because of the ease with which insulin is destroyed by digestive ferments that the discovery of the relation of the pancreas to diabetes was not followed earlier by the successful application of this knowledge to the treatment of this disease. It was only when a way was shown of protecting the active principle (insulin) against the digestive ferments during extraction and of giving it by injection that success with it was achieved. Favorable reports after oral administration of pancreas preparations have been assiduously collected by the promoters of these nostrums; but, in view of the frequently erratic course of the disease and the lack of sufficient scientific control in these reports, they cannot be seriously considered as invalidating the solid body of facts that deny the efficacy of oral therapy."

Now it is as useless to affirm as it is to deny. My own opinion is, perhaps, worth nothing to those who disagree with me; but to me it is worth far more than their opinions! During the twenty years that I have followed this subject, I have seen clinical case after clinical case and laboratory finding after laboratory finding that give me the confidence that I have in oral pancreas therapy.

Here again we have the same state of affairs that has been noted in connection with other moot points about organotherapy referred to elsewhere. The criticism of oral pancreas therapy is, as expressed in the quotation above, based on the undoubted fact that "insulin is destroyed by digestive ferments." True, insulin is capable of maintaining carbohydrate metabolism, but diabetes is not merely hypoinsulinism, neither is the oral pancreas product insulin.

Exactly the same thing occurred to bring about the impasse between the physiologists and the clinicians with regard to adrenalin and the adrenal cortex (9), parathyroid therapy (see quotations from McCann on page 152), and the "supposititious pituitary influence" (page 53).

However, I shall take little space here for the "assiduously collected" good reports, but instead will refer to some experimental work on animals that should put a different aspect on the subject.

Some of the experimental work with insulin needs to be reiterated in order to confirm its limitations. The questions to be answered are: (1) Does insulin suffice? (2) Are the activating pancreas principles destroyed by digestion? (3) Can the benefit from insulin be added to by oral pancreas therapy? All three questions are answered below in the reports from the universities of Chicago and Toronto.

Under the heading, "Can Insulin Replace the Pancreas?" the editor of the *Journal of the American Medical Association* (April 11, 1925, lxxxiv, p. 1122) refers pertinently to some of this research, as follows:

"Each successive discovery of an important physiologic hormone produced by a specific organ in the body has been followed by expectations that might readily be challenged on mature deliberation. The isolation of the highly potent epinephrine led many persons early to identify its physiologic action with the function of the suprarenal structures from which the product is derived. Similarly, thyroxin became synonymous in the minds of many with thyroid secretion; and often, recently, insulin has too hastily been supposed to represent the contribution of the pancreas. The test of all these hypotheses obviously consists in attempting to ascertain whether suitable administration of the isolated hormones in question will entirely avert such disaster or detriment as may ensue from loss of the glands that produce them.

"In the case of insulin, considerable disappointment attended the earlier trials. For example, Fisher, working at the University of Chicago, made numerous observations on totally pancreatectomized dogs. Through use of insulin they could be kept alive for some time, but the normal body weight could not be maintained; and, even when the insulin doses were so regulated that little or no sugar appeared in the urine, the polyphagia and some polyuria were present. Fisher consequently concluded that insulin probably does not represent the entire pancreatic hormone complex, since, in the total absence of the pancreas, insulin cannot maintain life or does not control all the diabetic symptoms, such as subnormal weight, polyphagia, and polydipsia. Fisher believed that the marked degeneration of the liver, and the extreme arterial sclerosis developed in dogs on long insulin management, indicate either diabetic processes not controlled by insulin, chronic toxic action of insulin itself, or such toxic action of the other substances in the insulin mixture.

"A clue to the difficulty seems to have been secured by the Toronto group, which also had earlier experienced these failures. By adding a daily allowance of raw pancreas to the diet, reenforced by insulin after pancreatectomy, the animals have been kept in a perfect condition of nutrition. Hence, it is concluded that the presence of something derived from the pancreas, either its digestive ferments or some internal secretion besides insulin, is necessary for the maintenance of normal metabolism. It is regarded as not unlikely that the

absorption from the intestine of toxic breakdown products of protein is responsible for the damage to the liver when no trypsin is present. In the human pathology of diabetes, it rarely happens that the external secretory function of the pancreas is entirely lacking; consequently, the extreme of experimental pancreatectomy represents a condition presumably almost never ensuing in human cases of insulin shortage."

The second report referred to here is the one made to the Society of Biological Chemists, by I. L. Chaikoff, J. J. R. Macleod, and J. Markowitz, of the University of Toronto, "Further Data on the Metabolism of Depancreatized Dogs Kept Alive with Insulin" (*Jour. Biol. Chem.*, Feb., 1925, lxiii, p. lxxi). They say:

"By daily feeding with raw pancreas (50 Gm.), along with flesh (200 to 400 Gm.) and cane-sugar (up to 50 Gm.), and the injection twice daily of about 16 clinical units of insulin, dogs weighing approximately from 8 to 10 kilos can be kept in a perfect condition of bodily nutrition. One animal is still living after fifteen months on this diet, and another after nine months. Since none of the symptoms of hepatic breakdown, previously reported from this laboratory (Allen, Bowie, Macleod, and Robinson) as occurring in the case of depancreatized animals fed without raw pancreas, have supervened, it is concluded that the presence of something derived from the pancreas, either its digestive ferments or some internal secretion besides insulin, is necessary for the maintenance of normal metabolism. It is possible that the absorption from the intestine of toxic breakdown products of protein is responsible for the damage to the liver when no trypsin is present."

From the foregoing we must answer our three questions as follows: (1) Insulin does not represent all the useful material found in the pancreas. (2) Pancreas by mouth is effective in experimental work. (3) The limitations of insulin control can be supplemented by oral pancreas therapy. Thousands of clinical experiences with various products confirm these answers.

There are a number of excellent pancreatic products available. Pancreatin is of some value, for it helps pancreatic digestion and thereby spares the pancreas. Holadin (Fairchild) has been used for twenty-five years with satisfaction, especially in elderly persons with obvious digestive stress. Pankreon is widely used in Germany, and on the continent of Europe many continue to use it in combination with insulin.

An oral preparation known as Trypsogen has been used for years as a means of increasing pancreatic activity in diabetes. It is a combination of a total pancreas extract with the ferments protected during manufacture, and a suitable dose of the bromides of gold and arsenic. The principal ingredient is given for its homostimulative effect upon the pancreas, and the gold and arsenic "for the purpose of depressing the hyperfunctioning adrenal system, the physiological antagonist of the pancreas." Referring to some carefully

controlled experiments with oral pancreas therapy, P. J. Cammidge, of London (*Brit. Med. Jour.*, Dec. 26, 1925, ii, p. 1216), says that Trypsogen "would seem to contain an antiglycogenolytic fraction which is absorbed from the alimentary tract."

In an attempt to explain the undoubted value of oral pancreas therapy, a writer in the *British Medical Journal* (May 12, 1928, i, p. 799) says:

"It is possible that these pancreatic extracts given by the mouth may stimulate some internal secretion other than insulin which aids in the utilization of carbohydrate within the body."

Undoubtedly, more than one hormone is produced by the pancreas, just as more than one hormone is active upon and through the pancreas.

DIABETES IN CHILDREN—The fatal character of diabetes in children has led to the suggestion that here there may be a pancreatic hypoplasia or atrophy, as compared with the more functional pancreatic damage in diabetic adults. Despite the presumed atrophy of the islets, insulin helps amazingly as long as it is continued, because it replaces the catalytic agent that cannot be supplied by the defective pancreas. The report by E. P. Joslin and P. White of experiences with more than three hundred children in a special diabetic clinic in Boston, indicates that insulin gives these youngsters an excellent chance to have a happy, useful life. Only one child is reported to have died during each year that the clinic has been in existence, whereas before the advent of insulin the majority of juvenile diabetics died. But, according to White (*Jour. Am. Med. Assn.*, Oct. 18, 1930, xcv, p. 1160), contrary to anticipations, no evidences of basic improvement in the pancreas are found even in the most carefully treated diabetic children.

Neither is pancreatic support of any avail. My own experience indicates that oral pancreas therapy, which is often used with real benefit in the treatment of diabetes mellitus in adults, is particularly useless in children. This is explained by the fact that this method depends upon the response of the patient's own pancreas for any benefit that it may have, thus differentiating between its therapeutic prospects in diabetic children and adults.

DIABETIC GANGRENE—Most of the cases of gangrene encountered in general practice are the sequel of diabetes mellitus. Every case is studied from this view-point and, where hyperglycemia and acetonuria are found, the treatment is that of diabetes. When gangrene develops in other circumstances, as following acute infectious diseases such as scarlet fever, typhoid, or erysipelas, it is a mechanical process, just as is gangrene of the lung or that which may develop in thrombo-angiitis obliterans. Such anatomical

difficulties do not lend themselves to endocrine therapy, but, in our consideration of these patients, we should remember that the endocrines have much to do with the immunity responses of the body. (See Immunity—68.) In the gangrene of diabetes, however, organotherapy offers possibilities of prompt and complete benefit. For years before insulin was perfected, pancreas organotherapy had proved itself of value in gangrene.

That the pancreas plays an important part in preventing or controlling infection has definitely been proved. In the experiments of E. Hédon, of Paris (1890), as well as in those of von Mering and Minkowski (*Arch. f. exper. Path. u. Pharmakol.,* 1893, xxii, p. 271), and many others, it was found that the removal of the pancreas in one step was almost invariably fatal. The animals did not die of shock or loss of the digestive organ, but from severe sepsis—the wound did not heal. E. H. Starling ("Principles of Human Physiology," Philadelphia, Lea and Febiger, 1926, p. 687) draws attention to this in the following statement:

"Owing to the fact that the tissues of a diabetic are extremely prone to infection, it is often difficult after total excision of the pancreas . . . to procure healing of the wounds without suppuration."

Pancreatic support with organotherapy is just as reasonable as adrenal support or other endocrine encouragement to which we are accustomed. It is possible to interfere with the dyscrinism underlying gangrene. The following human-interest story may add to the conviction that even ultimate conditions of this kind are not beyond hope. This experience was told to a group of physicians in Detroit. I reported it (*Hormone,* Jan., 1929, v, p. 9), and the doctor who told the story has verified it:

"The leading bootlegger in Detroit—or one of them!—came to me and asked me to get his father into a certain hospital as he was seriously ill and could not be treated at home.

"I made arrangements by telephone and before I could get out to visit him, the superintendent of the hospital called me and asked me if I couldn't take the man away. I demurred, but went to the hospital at once. There I found an emaciated old man, past seventy, with gangrene of the scrotum involving an area larger than my hand. The condition was far advanced and it looked as though we could do very little good. The odor was terrific, and that was the cause of the superintendent's perturbation. Incense was being burned in the room almost constantly.

"The patient was, of course, a diabetic. All the tests were made repeatedly —urine, blood sugar, acetone, etc.—and all the reports are on record.

"The treatment consisted of iodoform dusted on the raw area, and Pan-Secretin Co.,* 2 tablets four times a day, with nothing else—no insulin at any time and no special dieting except the omission of sweet desserts. Instead of dying in a few days as we all naturally expected, our patient began to

improve, the area to heal, and the sugar to decrease. To make a long story short, the gangrenous scrotum was entirely healed in two months, and the patient lived in fair health until almost a year later, when he caught cold from sitting by an open window, developed pneumonia, and died."

This is far from being the first case of diabetic gangrene that has healed after a comparatively short course of treatment with pancreas therapy.

RECAPITULATION—What is the essence of this matter, and how does it differ from the "accepted" therapeutic routine in diabetes?

1. Diabetes is more than carbohydrate intolerance and hyperglycemia; it is a sympathetic, digestive, toxic dyscrinism involving the duodenal and adrenal internal secretions, besides the pancreas itself.

2. The endocrine treatment of diabetes must include far more than simple replacement therapy (with insulin), for insulin is but a part of the pancreatic internal secretion just as thyroxin is but a part of the thyroid internal secretion.

3. Pancreatic support may be accomplished by sparing the carbohydrate metabolic mechanism by two forms of organotherapy—substitutive (insulin) and homostimulative (by the use of total extracts of the pancreas tail and duodenal mucosa, or the combination of these known as Pan-Secretin Co.*). The former performs the essential part of the work that the pancreas should have done, while the latter assists the pancreas to do better its two duties, digestive and endocrine. Insulin is of undoubted symptomatic value, rapid but temporary in its influence, while this formula is much slower in action and depends upon the responsiveness of the pancreas for any benefit that may follow.

4. A differentiation is made between functional and organic pancreatic dysfunction just as differences are made between hypoadrenia and Addison's disease (35), or between minor hypothyroidism and myxedema (67). It is believed that diabetes in children is an atrophic structural disease, while in adults it is more of a functional depletion. This makes a great difference in the treatment of diabetes in the young and the middle-aged.

5. The treatment of diabetes is not yet broad enough. Besides necessary dietetic control and the artificial supplying of insulin, we must spare the pancreas from every other angle possible—emotional, infective, toxic. We must balance the other factors in the endocrine upset, encouraging secretin production, overruling sympathetic irritability, and enhancing the hepatic detoxication. Then, perhaps, there may be a change in the vital statistics.

53. DIGESTIVE DISORDERS

Achylia Gastrica — A Muscle Digest in Therapy — Apepsia Interferes with Organotherapy — Biliary Insufficiency — Colitis — Constipation — Diarrhea — Dyspepsia — Intestinal Stasis — Nervous Indigestion — Sprue.

THE CONSIDERATION of digestive disorders from the endocrine standpoint is appropriate for two main reasons: (1) Distinct disturbances of one or several phases of digestion are found with several of the major endocrine disorders; and (2) improvement in digestion often accompanies the response to organotherapy for a given dyscrinism. To this may be added the well-known fact that certain endocrine measures are decidedly helpful in the direct treatment of a number of digestive irregularities.

Indigestion is common in both forms of dysthyroidism: In hyperthyroidism the indigestion may be associated with periods of diarrhea of gastric origin, while in hypothyroidism it is accompanied by the most intractable type of constipation. Hypopepsia, which is the rule in Addison's disease, is often found with vomiting, gastric crises, and periodic diarrhea. The digestive features of diabetes are marked but variable; indigestion is a serious factor and indeed may be an important part of the etiology. Diabetes mellitus is essentially an exaggerated form of indigestion in which stress upon the pancreas over a period of years has finally broken down both its digestive and endocrine functions (52).

ACHYLIA GASTRICA—No matter what the actual cause of achlorhydria, apepsia, or true achylia gastrica, there is plenty of evidence to incriminate it as a part of the etiology of several serious nutritional disorders. Whether the difficulty is an organic one, involving complete inability of the gastric glands to produce their digestive elements, or whether the difficulty is a functional and temporary one, defective gastric digestion initiates a train of symptoms that are far more important than the digestive upset that shows itself in gastric fermentation, slowed emptying of the stomach, etc.

Some very informative speculations connecting achylia gastrica with the etiology of pernicious anemia are being discussed. A brief consideration of the work of W. B. Castle, of Harvard University (*Am. Jour. Med. Sc.*, Dec., 1929, clxxviii, p. 748), may be of interest here. Castle experimented on several cases of pernicious anemia with prominent digestive symptoms. Healthy persons would eat a certain amount of beefsteak and then permit it to be removed from the stomach after varying lengths of time (usually from forty-five minutes to an hour) so that it could be given to these anemic patients. This artificial digestive service brought about not only improve-

ment from the standpoint of nutrition, but also marked and prolonged remissions in the blood findings. For example, eight of ten patients showed "marked clinical improvement" within a week. Characteristic increases in the reticulocyte counts were noted, and the improvement was progressive. In three cases, the red blood-count showed a gain of 2,000,000 within two weeks! Castle says that the response occurring in these eight patients treated with the regurgitated material "was entirely comparable with what might have been expected with moderate uniform daily doses of liver." He concludes his interesting report with the suggestive statement:

"In contrast to the conditions within the stomach of the pernicious anemia patient, there is found within the normal stomach during the digestion of beef muscle some substance capable of promptly and markedly relieving the anemia of these patients."

A MUSCLE DIGEST IN THERAPY—Based on Castle's conclusions, some experiments were carried out with a digest of beef muscle in vitro instead of in vivo, for one could not hope to develop a method of treatment that depended upon the services of professional digesters!

The outcome of the attempt to materialize this idea is called Myogestin.* It consists of beef muscle digested with a suitable proportion of an emulsion of stomach linings, with additional hydrochloric acid to make the pH normal, or 0.6 per cent. After digestion, the mixture is centrifuged, the filtrate brought to dryness, and the solid débris discarded.

Since this preparation was made available, C. C. Sturgis, of the University of Michigan (*Jour. Am. Med. Assn.,* Aug. 23, 1930, xcv, p. 585), also found that, if beef muscle is fed to a healthy man and then removed after it is partially digested, and fed to a pernicious anemia patient, a remission of the anemia is induced. He learned that similar results may be obtained if the beef is digested in vitro. As a digestant, we have found stomach emulsion more satisfactory than gastric juice, because there undoubtedly is a hemopoietic principle in the stomach tissue itself (22).

It is postulated by Castle that, during the normal digestion of protein in the stomach, certain elements are produced that not only are necessary to efficient digestion and assimilation of food but have to do with the physiological process of hemopoiesis.

Myogestin is not recommended to replace liver extract, although it undoubtedly is an effective hematinic. It is a supplementary measure for use in the serious gastric disorders of pernicious anemia because it is a food as well as a gastric agent.

APEPSIA INTERFERES WITH ORGANOTHERAPY—There is another important aspect to the subject of achylia that has to do with the relation that gastric indigestion bears to the assimilation of organotherapeutic products given by mouth. Many early endocrine preparations were desiccations of glandular tissues freed from water in vacuo and defatted by suitable fat solvents. Administered in the form of capsules or tablets, this material was virtually a form of specialized diet; the term "glandular feeding" is still very common. Endocrine preparations must be digested before they can be assimilated and the active principles contained in them absorbed. A careful study of a number of endocrine patients with achylia gastrica indicates that this digestive disorder militates seriously against the clinical efficacy of the needed organotherapy. In other words, anything that interferes with the complete digestion and assimilation of endocrine desiccations interferes with the expected service from the hormones. By assisting digestion, as with hydrochloric acid with or without pepsin, the efficacy of organotherapeutic remedies is often increased materially in patients with alimentary insufficiency who had not previously responded well to organotherapy.

This point, which can be verified easily, emphasizes the absurdity of attempting to interfere with the digestion of glandular preparations by recourse to salol or other enteric coatings. When "protected" in this way, the tablets are merely kept from digestion for an hour or so, for obviously they must be digested in order to be active, and hence that digestion is carried on in the intestine. It seems that destruction in the intestine by the pancreatic juice in an alkaline medium does not differ materially from that brought about in the stomach by pepsin in the presence of acid.

It has been suggested that the gastric acid interferes with the potency of endocrine products given by mouth. Experience with organotherapy in patients with achylia certainly does not confirm this. Besides, there is no evidence that the acid concentration in the stomach is any more destructive than the alkaline concentration in the duodenum.

BILIARY INSUFFICIENCY—It should be unnecessary to explain the physiology of bile production and its influence in the intestine. The hepato-biliary function is apparently a means of removing from the liver, by-products of hepatic cellular activity with which are several substances of decided utility in the intestine. Biliary stasis involves mechanical interference in the function of the liver cells, and a corresponding mechanical facilitating of disease of the gall-bladder, and the production of gall-stones.

The effect of the bile in the intestine is particularly important. On mixing with the half-digested food in the upper intestine, it serves three purposes:

(1) It neutralizes the acid chyme to prepare the material for digestion by the pancreatic ferments; (2) it quite definitely antagonizes the growth of the putrefactive bacteria in the bowel; and (3) it apparently has a definite effect on the function of the intestinal walls, particularly as regards the production of mucus. This is quite an important matter, which has not received the appreciation in this country that it deserves.

About twenty years ago, Henri Roger and his associates in Paris reported some very interesting work, the essence of which has come to be known as the mucinase theory. The idea, briefly, is this: Normally the intestinal walls secrete a ferment called "mucinase," a function of which is to coagulate mucin. This ferment is rendered inactive by certain alcohol-soluble, heat-stable substances in the bile. Since mucous colitis so often is associated with biliary insufficiency and may be produced experimentally by diverting the bile flow from the duodenum, Roger inferred that the membrane formation is due essentially to insufficiency of bile. Later, mucinase was actually isolated from the feces of patients with mucous colitis. Many physicians have proved this both clinically and experimentally. H. Nepper, of Paris, concludes from his clinical results that mucomembranous colitis is due to *oligocholie* (bile insufficiency) and cannot exist without it. He insists that the membrane formation results from the abnormal increase in the mucinase and from a relative and simultaneous diminution of the amount of bile, and especially its anticoagulating power, which permits the mucinase secreted by the intestinal epithelium to coagulate the mucus.

More than three thousand years ago, it was suggested that bile from a hedgehog killed during a certain quarter of the moon be used for indigestion, and ox-gall has been used empirically in many places for centuries. We now know that the principal therapeutic value of bile lies in its salts, sodium taurocholate and sodium glycocholate. These are organotherapeutic products, although they do not act as do the hormones. After rendering the services already mentioned, the bile salts normally produced in the liver are absorbed with the food, enter the portal vein, and are returned to the liver, where they are used over again. Therefore, the administration of bile is a means of increasing the total amount of bile salts supplied to the liver to be made into bile.

Biliary organotherapy causes quite remarkable benefit in conditions of biliary stasis. The liver is "wrung out," and the increased bile flow is mechanically advantageous, although it cannot wash away stones impacted in the gall-bladder. It is a peculiarly valuable means of sweetening the intestine.

The production of bile can be augmented very materially by the use of bile salts. There are a number of references in the literature telling of large increases—from 100 to 300 per cent.—in the amount of bile passing from the gall-bladder through a drainage tube, under the influence of varying doses of bile salts.

The advantage of this method of treatment is promptly obvious in all conditions in which there are hepato-biliary stasis and alimentary putrefaction. Attention is directed to a suggestive outline that includes biliary organotherapy in Chapter 104.

COLITIS—A comprehensive outline for the treatment of mucous colitis was published by me in *American Medicine* (Sept., 1928, xxiii, p. 678), from which some points will be submitted here:

Colitis is a peculiarly resistant and common disorder because the colon is the most abused organ in the body. The factors that contribute to this particular disease are digestive, infective, chemical, and mechanical, and no treatment can be successful unless it is directed at all these phases. For example, if there is an infestation in the colon, obviously dietetic regulation alone will fail. If there is a mechanical defect—as there is so many, many times—mechanical measures must be used. If, as we shall soon see, there is a definite glandular phase, it cannot be controlled effectively unless the other features are cared for simultaneously.

Hence the treatment of colitis with its varying manifestations is usually a failure in the hands of the general practitioner, simply because he is not in a position to give persistent, protracted attention to all these matters. On the other hand, the specialist who lives in an atmosphere of colons, may be able to accomplish most encouraging results in the treatment of many long-standing cases. It is planned to emphasize here those features of the subject that have a bearing on endocrinology.

The greatest source of trouble in the alimentary canal undoubtedly is the liver. Defective hepato-biliary service causes a train of circumstances that inevitably ends in colitis. The mucinase theory of Roger, to which attention has just been called, is really an important matter, and its influence on the causation as well as the continuation of colitis comes about in several definite ways: (1) The alimentary putrefaction that proceeds unchecked when there is a deficiency of bile permits the growth of organisms, the waste products of which definitely irritate the alimentary walls; (2) the chemical influence of the ferment mucinase, as outlined, permits the accumulation of mucus, which normally should remain in such form that it can serve as an efficient lubricant; but instead the lubricant becomes a thickened, bacteria-ridden

blanket that accentuates the irritation; (3) the mechanical conditions, due to the shortage of bile, cause the alimentary contents to remain in the bowel much longer than normally. The most important feature of the treatment of colitis is, by all odds, the hepato-biliary one.

There are several definitely endocrine aspects to colitis: Muscular atonicity supplements the static state of affairs just referred to. The tone of unstriped muscle is under the control of the adrenal glands. Adrenal cortex therapy can be used with really remarkable effects in intestinal stasis, as we shall soon see. Again, as is shown in the consideration of constipation, there is a very important thyroid aspect to many of these cases. Without attention to this, the most scientific, persistent, and well-directed regimen for the treatment of colitis inevitably will fail if the patient is suffering from hypothyroidism and if the bowel walls are infiltrated and boggy, as so often is the case in marked degrees of hypothyroidism. An unnoticed hypothyroidism will invariably interfere with the best treatment of mucous colitis.

There are a number of references in the literature to the importance of ovarian dysfunction as a contributory factor in colitis. This, I believe to be due to influences that are brought about through the associated glands, notably the thyroid. In other words, dysovarism causes an upset in the thyroid function which produces changes that influence the entire body, including the intestinal walls. Many physicians who have made a special study of colitis have discovered that it is possible to hasten the success of their treatment and establish its benefit more permanently by controlling the associated functional disturbances in the ovaries. In fact, several of my friends use Adreno-Ovarian Co.* routinely as a part of their treatment of colitis, if there is the slightest manifestation of dysovarism. It is given for at least half the month, the dose being pushed prior to the expected flow and continued for several months.

Obviously these various forms of organotherapy cannot influence the infective, digestive, chemical, or mechanical features of this complex disorder. On the other hand, it is equally true that no other measure, no matter how effective, can be expected to control the endocrine phases of these cases. To be successful, any treatment of colitis must be comprehensive and persistent.

There is another phase of colitis that one finds in ultimate cases—ulceration. Ulcerative colitis calls for a consideration of all the factors that have been suggested already, and we can add still one more measure that may make a great deal of difference to the outcome. Some years ago, W. F. Koch and other workers in the University of Michigan showed that the parathyroid glands have a marked influence on the destruction of certain toxic substances, of which guanidine is a type. Guanidine is one of the products of alimentary

putrefaction and is a particularly poisonous protein-split product. It stresses the liver, and R. H. Major, of Kansas City, and several other workers have shown that it has a remarkably active depressor effect (13).

This opens up still another phase of the organotherapeutic possibilities in chronic mucous colitis. Most sufferers from mucous colitis do not have their tissue cells in good condition to offer resistance. They are toxic, are suffering from a depleted endocrine mechanism, and their immunizing response is far below par. Because of its calcium-regulating powers, parathyroid is believed to increase resistance. Carl A. Dragstedt, of Chicago (*Jour. Lab. and Clin. Med.,* May, 1928, xiii, p. 732), remarks that

"Parathyroid administration is an aid in the fight against infection of the chronic type, not by its specific action on the infecting organism, but because it places the tissue cells under the most favorable condition for an adequate resistance."

Chronic ulceration (95) offers one of the most real possibilities for parathyroid therapy. H. W. C. Vines and his associates at Cambridge University first showed that parathyroid by mouth aids the cellular chemistry so that the healing powers of the body are stimulated even though years of other treatment may have failed. In other words, oral parathyroid therapy encourages the healing of ulcers, and already a number of writers have called attention to the advantages of this treatment in ulcerative colitis.

B. Haskell and A. Cantarow, of Philadelphia (*Am. Jour. Med. Sc.,* Feb., 1931, clxxxi, p. 180), report some extended studies of the non-specific form of chronic ulcerative colitis. Their clinical investigations consisted in the observation of thirteen patients who were treated with calcium and parathyroid. Three continued treatment for only four weeks and were not followed up. Of the other ten, two have been well for three years, two for two years, four for from one to one and a half years, one was greatly benefited, and in only one was the treatment unsuccessful.

The treatment included: (1) a cellulose-free, non-irritating diet; (2) belladonna and kaolin; (3) calcium salts, ammonium chloride, and parathyroid. The calcium was given in the form of the chloride, lactate, and gluconate, the latter being perhaps the best tolerated. As these authors say, the function of the parathyroids "appears to be that of a regulator of calcium metabolism, and its action is primarily as a calcium mobilizer." Parathormone was injected intramuscularly at intervals of from forty-eight to seventy-two hours, the usual adult dose being from 20 to 30 units, depending upon body weight. These authors conclude:

"Our investigations into the action of parathyroid extract suggest that

its injection results in an increase in the availability and utilization of calcium, as well as in a tendency toward the restoration of a normal ratio of diffusible to non-diffusible calcium. . . . The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the beneficial effect of calcium on the following existing conditions: (a) nutritional changes in the tissues, with or without a disturbance of calcium partition; (b) spasticity of the colon; (c) hemorrhage."

In view of the numerous measures available in the treatment of colitis, it may be well to summarize the suggested therapy:

(1) Unload the bowel and keep it that way by mechanical means.

(2) Rest the bowel by physical rest, which is very necessary for these exhausted patients, and by withholding foods and food combinations that stimulate and irritate. This is the outstanding reason for the non-residue diet (102).

(3) Encourage the liver from the standpoint of both detoxication and bile production (104).

(4) Change the flora by measures calculated to modify the reaction of the alimentary condition. This can be done by *B. acidophilus* therapy and more efficiently by the administration of lactose in such form as will reach the colon (Colactin).

(5) Organotherapy: Parathyroid in case of ulceration; thyroid where there is obvious hypothyroidism and dysovarism; Adreno-Cortin* for its musculotonic effect; pluriglandular therapy for the thyro-ovarian-pituitary upset so commonly associated; Anabolin* for its detoxicative hepatic effect.

(6) Heat is the most valuable of all the physical measures, because it increases circulation, encourages function generally, antagonizes irritation, and relieves atonicity.

CONSTIPATION—The endocrine basis of constipation is nowhere more obvious than in the treatment of dyscrinism in children. One of the first salutary changes following the administration of thyroid to cretins, or of Antero-Pituitary Co.* to an endocrinopathic child, is the improvement in the condition of the bowels. Attention is often called to the vital influence of the thyroid hormone upon the cells. The condition known as thyroid infiltration is of tremendous clinical import. In various parts of this book the reader will find indications that infiltration of the middle-ear may result in deafness (54); that infiltration of the bladder wall may cause frequent micturition at the menopause (67) and nocturnal enuresis in children (46); that cellular infiltration may, in a definitely mechanical way, cause menorrhagia (80), nephritis (86), and even neuritis (78). It is not unreasonable,

then, to suppose that there is an alimentary infiltration associated with hypothyroidism. Constipation is a condition almost pathognomonic of hypothyroidism. Every constipated patient should be considered from the thyroid standpoint, although, of course, there are other evident causes of constipation.

In a French book, the translated title of which is "Minor Thyroid Insufficiency and Its Treatment" (Paris, O. Doin et Fils, 1913, p. 88), Léopold-Lévi and Baron H. de Rothschild point out that several arguments demonstrate the existence of a true hypothyroid constipation, *viz.*:

"(1) Its habitual presence in human myxedema; (2) the effects of thyroid treatment of constipation; (3) the production of diarrhea by alimentary thyroidism; (4) the presence of diarrhea during the course of Basedow's disease. Constipation may be classed among the disturbances arising from hypothyroidism, and the results of thyroid treatment constitute the most interesting feature. . . . Thyroid constipation is chiefly an ordinary constipation, and no objective sign permits any differentiation. It is met in both sexes and at all ages.

"Prior to the application of any treatment, we may assume the presence of thyroid constipation from: (1) coexistence of constipation with other symptoms or syndromes of dysthyroidism; (2) the appearance of the constipation at the moment of certain hypothyroid attacks; and (3) the frequency of thyroid constipation.

"This form of constipation is perhaps the most frequent one. It coincides with chronic rheumatism, migraine, asthma, dermatosis, neurasthenia, and neuro-arthritism of thyroid origin. It is frequently met in benign chronic hypothyroidism, coincides with goitre, etc.

"It must not, however, be supposed that all cases of essential constipation are of thyroid nature, nor that constipation necessarily forms part of the hypothyroid picture. Even myxedematous subjects may not be constipated, all functions not being uniformly affected in all hypothyroid subjects.

"On the other hand, on the ground of absence of results of treatment in a case of constipation, one must not conclude that there exists a non-thyroid constipation. We may, therefore, conceive a thyroid constipation that cannot be modified by means of thyroid therapy.

"Constipation occurs more frequently in women, thyroid pathology being especially feminine by reason of the relations existing between the thyroid and the ovary; the influence of menstruation upon constipation may cause either aggravation or disappearance of the latter. . . . Perhaps even the effect of emotion upon the intestine may not always make itself felt in a direct manner, but may involve participation on the part of the regulative glands, such as the thyroid.

"It may be concluded that constipation is a thyroid sign, and that *thyroid treatment is rational treatment of essential constipation.* It acts upon the intestine not only during the course of its application, but its effects are

generally lasting. Furthermore, it acts upon the temperament of the subject and thus may dispel symptoms such as migraine—sometimes wrongly ascribed to constipation, but which are really simultaneous symptoms arising from a single and more general cause."

DIARRHEA—Irritation of the bowel due to toxins not disposed of because of hepato-biliary defects may cause diarrhea. This symptom may supervene in the ultimate stages of Addison's disease, and is common in advanced cases of hyperthyroidism. In fact, both ultimates of dysthyroidism may cause diarrhea. Quoting again from Léopold-Lévi and de Rothschild's book (*ibid.*, p. 96):

"As regards diarrhea, this may have its cause in alimentary dysthyroidism. It forms part of the symptomatology of Basedow's disease, and in this disorder does not admit the idea of any pancreatic insufficiency. The reason we mention diarrhea is that, although it is of a hyperthyroid character, it is, in certain cases, possible to suppress it by thyroid treatment. In such cases, we are dealing with intestinal thyroid instability, and thyroid medication regulates the intestine.

"These cases may be divided into three categories: (1) thyroid instability with diarrhea resulting from continued intestinal disorder; (2) intestinal hyperthyroidism caused by heat-stroke, for instance (these cases are somewhat similar to hay-fever and spring dyshidrosis); (3) thyroid instability, with alternating intestinal disorders (constipation, diarrhea). Here, too, thyroid treatment regularizes the intestinal condition."

DYSPEPSIA—What has dyspepsia to do with dyscrinism? More than many of us have thought, for there is a quite definite type of dyspepsia due to the mechanical difficulties brought about by the cellular infiltration of hypothyroidism, which already has been discussed.

A. H. Bunce, of Atlanta (*South. Med. Jour.*, Feb., 1929, xxii, p. 119), states that achlorhydria and anemia may be produced both clinically and experimentally by insufficient thyroid secretion. In a series of twenty-three patients with an average metabolic rate of minus 30.5, achlorhydria was found in 25 per cent. Bunce also cites a case in which the presence of both anemia and achlorhydria aroused suspicions that pernicious anemia was being dealt with, and which, though it failed to improve under liver therapy, rapidly improved when 6 gr. of desiccated thyroid was administered daily.

The sympathetic upsets that are related to the emotions are essentially endocrine in character. What is the cause of the acute dyspepsia that follows a shock, bad news, or an accident? The stomach is not defective—it is merely the victim of circumstances that are largely endocrine-sympathetic in nature.

Chronic dyspepsia causes a train of symptoms that produce or are associated with gastric atony or dilatation, alimentary atonicity, and stasis—a typical muscular problem. The effect of the adrenal cortex hormone on the muscular chemistry and through it on muscle tone can be utilized with prompt effect on the muscle aspects of dyspepsia and general indigestion. One of the coincidental advantages from the use of Adreno-Cortin* in conditions of hypoadrenia is a noticeable increase in alimentary tone. Many physicians are using this new principle for this very purpose, as will be noted in the consideration of intestinal stasis (see pages 59 and 404).

Again, dyspepsia often seems to be ovarian in character. A woman with dysovarism complains that her digestive troubles are periodic, being much worse near the menses. Surely the regulation of dysovarism is indicated whether it is related to the dyspepsia or not. The following interesting case demonstrates how the endocrine imbalance of a minor dysovarism may cause a serious digestive upset:

A young lady of twenty, after having suffered from chronic indigestion for years, with a resulting malnutrition and neurasthenia, spent six weeks in a hospital under the care of one of Philadelphia's leading gastro-enterologists. The best treatment directed at her alimentary difficulty gave her relief for just three months—only twice as long as the period of intensive treatment. Then her trouble returned, and she was back where she was before. Another physician, much concerned because of the numerous failures of the past, gave consideration to the fact that she did not menstruate normally. Her periods were delayed and scanty, though she felt no special discomfort and had never been considered from the menstrual standpoint. The malnutrition previously credited to the indigestion was now studied more carefully from a thyroid angle, and the conclusion was reached that thyro-ovarian therapy might reasonably be given for several months. It was, and the patient was cured entirely—indigestion and all—within two months. The physician said, "This, more than any other experience, convinced me how important these endocrines really are."

The conclusion to be drawn from this case is simple: In view of the direct and indirect endocrine influences upon the gastro-intestinal functions, problem cases with dyspepsia surely deserve consideration from the endocrine standpoint. When there is evidence of definite endocrine defects, the treatment should include the needed organotherapy—thyroid, thyro-ovarian, etc. When conditions suggest that endocrine aid may be symptomatically helpful, add it to the treatment. The increased function, as in the effect of cortical extract upon muscular tonicity, can be only beneficial even though it is not the principal part of the therapy, which must always be directed at the stomach and its contents.

INTESTINAL STASIS—As natural sequences of simple constipation, both intestinal stasis and ptosis require consideration from exactly the same point of view. However, the patient with stasis may not be especially costive, for the bowels may move daily. I frequently use my pocket pencil to illustrate this to patients.

Recent research with the adrenal cortex hormone has shown that bilaterally adrenalectomized animals invariably have intestinal stasis of ultimate degree (9). The muscular atonicity caused by hypoadrenia is so complete that these cats can neither swallow nor defecate. Peristalsis is virtually stopped. Injections of Adreno-Cortin* prevent this condition and maintain an apparently normal muscle tone.

Among the earliest clinical users of this product were several patients with asthenia of maximum degree. As would be expected, all of them had stasis. Adreno-Cortin improved the general as well as the alimentary muscle tone.

Later, when the supplementary oral product was perfected (*i.e.*, when the total extract had been suitably de-epinephrinized), it was given to many patients, with improvement. One of the peculiarities of this treatment has to do with the alimentary effect—in a number of cases the dose could not be increased beyond a certain point because it caused cramps in the abdomen. This is not a uniform result, some patients responding in this way sooner and to a much smaller dose than others.

This alimentary effect of the adrenal cortex hormone is undoubted, and the explanation seems clear enough—the product is a catalyst to the muscular chemistry; it increases the physiology of the muscles, thereby improving their tone and antagonizing local and general fatigue. Several gastroenterologists have found this new principle of decided supplementary service. (See page 59.)

NERVOUS INDIGESTION—In his recent book ("Nervous Indigestion," New York, Paul B. Hoeber, Inc., 1930, p. 33), Walter C. Alvarez, who left San Francisco to lend additional prestige to the staff of the great Mayo Foundation, says:

"Nervous indigestion is a convenient term with which to designate all the gastro-intestinal disturbances for which no organic cause can be found. Not infrequently this diagnosis can be made with confidence as soon as the patient has talked a few minutes, but more often it is made by a process of exclusion, after every other type of disease has been thought of and ruled out."

After an evening with this highly interesting book, I cannot get away from the impression that many of the cases that Alvarez labels "nervous indiges-

tion," for which no organic cause can be found, are really endocrine cases. As one sees what attention is paid to neuroses, emotions, sympathetic upset, hysteria, and the like, the opinion gains ground that the endocrines *are* involved in most of them. And why not, when the connection between the endocrines and such disease pictures as neurasthenia, psychasthenia, sympathicotonia, and vagotonia is such a close one?

Summing up the subject, we may say that there is no single endocrine remedy for digestive disorders, but there are many endocrine helps for dyspeptics with endocrine troubles!

SPRUE—The chronic endemic enteritis of the tropics is known variously as sprue, psilosis, and alimentary moniliasis. China seems to be the center for this disease, which attacks visitors with greater intensity than it does the natives.

Sprue is a chronic digestive depletion with watery, frothy diarrhea caused by the implantation in the intestines of the fungus *Monilia psilosis,* which ordinarily cannot live in the presence of normal digestive action. The indigestion permits the colonization of these spores, and the combination causes a serious picture which usually includes a very sore mouth, an excoriated tongue, alimentary ulceration of varying degree, and a progressively severe malnutrition.

In February, 1923, H. H. Scott, then of Hongkong (*China Med. Jour.,* July, 1923, xxxvii, p. 581), made a preliminary report to the Royal Society of Tropical Medicine, advocating the use of calcium lactate and parathyroid in the treatment of sprue. Several other papers have appeared outlining a number of cases of sprue of varying degrees of severity. As a result of his experience, Scott is able to compare this new treatment with the ordinary methods. It is evident that the underlying influence of the parathyroids on healing, as has been discussed elsewhere (95), applies in the ulceration of the alimentary canal that is typical of sprue. After a detailed discussion of a number of his clinical experiences, Scott (*Brit. Med. Jour.,* Aug. 23, 1924, ii, p. 305) remarks:

"The above contrasted cases suffice to show that with the administration of calcium and its regulation by parathyroid, the disappearance of symptoms occurs early, the ionic calcium returns rapidly to normal, ordinary diet can be resumed in a shorter time, and the beneficial effects are generally steady and permanent. . . . As a rule it has been found that the fuller diet provides all the calcium needed, and this element can be first left off, the regulator—parathyroid—being continued in full doses for another week or so. (One-tenth gr. two or three times a day.) This is then reduced, and, as a rule, can be stopped in its turn from a week to a fortnight later."

Sprue is often associated with serious nutritional anemias that have even been mistaken for pernicious anemia. In view of this, liver therapy has frequently been added to other indicated treatment of sprue. It is interesting to note that these clinical opinions are now confirmed by a number of writers. For example, A. L. Bloomfield and H. A. Wyckoff, of San Francisco (*Am. Jour. Med. Sc.,* Feb., 1929, clxxvii, p. 209), report on the use of liver extract in two cases of sprue:

"The diagnosis of sprue as against pernicious anemia was based on the presence of considerable amounts of free HCl in the stomach juice, the character of the stools, the absence of neurologic changes, and (in one case) residence in the tropics. Responses similar to those usually obtained in pernicious anemia resulted, with rise in reticulocytes, increase in blood-count, and improvement in gastro-intestinal symptoms with gain in weight and general well-being. Incidentally, it has been pointed out that the typical response may be obtained after a single large dose of liver extract as well as after daily smaller doses. The results are additional evidence of a close relationship between sprue and pernicious anemia."

Again, G. C. Low and W. E. Cooke, of London (*Lancet,* Nov. 5, 1927, ccxiii, p. 960), discuss the treatment of sprue; but fail to stress Scott's important discovery. However, they say:

"As regards the treatment of sprue generally, several points of interest may be mentioned: first, the use of liver extracts in the form of liver soup; and, secondly, the use of the so-called *pulvis bataviæ.*"

In the discussion that follows this paper, B. K. Ashford points out the remarkable efficacy of liver in the treatment of the so-called pernicious anemias of sprue. He traces the use of liver feeding in sprue back for thirty years or more.

An acceptable organotherapeutic routine for the treatment of sprue consists in Para-Spleen Co.,* 1, q.i.d., or 2, t.i.d., and Heparnucleate,* 4½ Gm. daily for from six to eight weeks.

54. EAR DISORDERS

General Care of the Deaf—Hypothyroidism a Factor—Cellular Infiltration Explained—Otosclerosis—Otitis Media—Tinnitus—Vertigo.

THERE ARE two broad types of deafness—organic and functional—and it is obvious that the organic cases cannot respond to remedies that are designed to modify functional derangements.

It happens that many cases of functional deafness have been caused by changes in the middle-ear structures which are quite similar, both in physics and chemistry, to those that are found in other structures of the body as a result of endocrine disorder. To put it pointedly, the nutrition and functional activity of the hearing mechanism are subject to influences that are under the control of the glands of internal secretion.

GENERAL CARE OF THE DEAF—Every otologist knows that the general health has a decided influence on the hearing of those whose hearing already is defective. Senility, which is generally agreed to be essentially a manifestation of hypocrinism (88), has a similar effect. Otologists also know that certain women with tendencies toward poor hearing are worse or better as they pass through the biochemical variations associated with the ovarian cycle.

Harold Hays, of New York (*Eye, Ear, Nose, and Throat Month.*, Nov., 1930, ix, p. 421), states that he is paying more and more attention to the general care of patients who are hard of hearing; in fact, he even advises hospitalization in many cases. He believes that "some general physical defect almost always can be found in deafened patients, and such defect must be taken into account and treated." In a more recent paper (*Clin. Med. and Surg.*, March, 1931, xxxviii, p. 183), Hays adds:

"I am eager to impress upon the family physician the fact that abnormal physical and mental states influence hearing acuity and, if one wishes to obtain any worth-while result, one must study each case as a separate entity and eliminate every factor. . . ."

Naturally, then, any factor such as those mentioned here, which is known to exert an influence on the aural structures, is doubly important.

HYPOTHYROIDISM A FACTOR—R. C. Moehlig, of Detroit (*Endocrinology*, May-June, 1927, xi, p. 229), specifically associates vertigo and deafness with hypothyroidism. This, of course, is in harmony with the suggestion made in the late nineties by Eugene Hertoghe, of Antwerp, who connected many functional disabilities in patients presenting *myxédème fruste* with the fundamental cellular infiltration that he showed was an essential feature

of all cases of moderately marked hypothyroidism. Moehlig refers to twenty-four cases of vertigo and deafness in patients with low metabolic rates. It is interesting to note that two-thirds of this series were females.

Thyroid therapy was used in sufficient dose to overcome the defective metabolism and other associated symptoms, and there was marked improvement in the majority of the cases that had not progressed to complete deafness. Moehlig's conclusion follows:

"Given a case of vertigo, with or without vomiting or fainting spells, ringing and buzzing in the ears, lessened or absent hearing, low or normal blood-pressure, and a low metabolic rate, in the absence of striking hypothyroid signs, we are justified in the conclusion that we are dealing with a unique and characteristic symptom-complex heretofore not appreciated as a clinical entity, and that the exhibition of thyroid in these cases may be expected to result in marked relief or complete cure."

Attention also is called by Moehlig to the report of R. A. Barlow, who made a study of the vestibular nerve function in fifteen cases of myxedema (*Am. Jour. Med. Sc.*, Sept., 1922, clxiv, p. 401). He emphasizes the delay in the response to stimuli that are found in these cases. Of course, all responses are slow in myxedema—mental, metabolic, physical—and naturally also those of the special senses.

CELLULAR INFILTRATION EXPLAINED—The sound philosophy of Hertoghe gives us a very good explanation of the mechanics of many of the responses to marked degrees of thyroid insufficiency. Despite the fact that this has been emphasized elsewhere, a brief reminder will be in order here:

The thyroid gland is responsible for the maintenance of the cellular chemistry throughout the body, and this obviously must include every functioning cell. When the catalytic agent that initiates these cell exchanges is lessened or lost, there ensues a slowing of the metabolism. This causes an accumulation of wastes which, by physical means, produce an absorption of fluids so that the specific gravity inside the cell will be equal to that of the other body fluids. This brings about a condition of infiltration or water-logging that is a serious detriment in many ways—from causing too frequent micturition (by denudation of the bladder mucosa) to hypertension (due to the mechanical interference of such infiltration in the so-called precapillary areas). These mechanical conditions undoubtedly may occur in the ear structures also.

OTOSCLEROSIS AND OTOLYMPHOSIS—Otosclerosis is a term that sometimes leads to misunderstanding because many cases so labeled are not really sclerotic, but merely infiltrated. Many specialists are beginning to consider the endocrine aspects of otosclerosis. Still another term has been used,

which is perhaps not unreasonable—otolymphosis. From it, we connote a form of lymphatic circulatory and cellular stasis that is the peculiarly outstanding feature of the tissues in ultimate hypothyroidism.

According to C. H. Muncie, of New York ("History of Deafness and Its Treatment," page 17):

"Otosclerosis is believed to be precipitated by a prolapsus of the eustachian tubes, which results in edema of the labyrinth followed by malnutrition of the internal capsule of the labyrinth, and leads to degenerative changes as the result of malnutrition. These cases, if seen before the degenerative stage, can be prevented, and many have had a substantial and permanent restoration of hearing."

Whenever a deaf person is found who exhibits the slightest reason for regulating a coincidental endocrine upset, this should be done as quickly and as thoroughly as possible. Even when deafness is in the early, non-organic stage, it is proper for the otologist to supplement all the indicated therapeutic measures with the coincidental control of any glandular disturbances that may be found, paying particular attention to the thyroid gland.

OTITIS MEDIA—Chronic otitis media sometimes proves to be a most stubborn disease. Since it is essentially an ulceration, why should not the fundamental idea that parathyroid therapy promotes the healing process in all forms of ulceration apply also to otitis media?

It is indeed possible to treat chronic running ear as a form of ulceration. Parathyroid therapy hastens the rate of healing in burns (42), ulcers of the leg (95), and sinusitis (76). This change is accompanied by two important developments: (1) There is an increase in the ionic blood calcium and a decrease in the blood coagulation time; and (2) the ulcerated area is changed in color and appearance, and the exudate is increased in amount and fluidity. This latter is *extremely* important, for the change in the activity in the ulcer is a prelude to healing. Hence *there must be suitable drainage.* Parathyroid therapy is contraindicated where there is pus without an exit—as in chronic appendicitis, pyelitis, and sinus or ear infections that are not adequately drained.

Many a physician has tried this form of organotherapy in chronic otitis when improvement was lagging and he did not know what else to do. This has been one of my chief trials, for a new idea in medicine usually is given a test in the most resistant cases. The philosophy that has made parathyroid therapy available in chronic sinusitis or sprue, in varicose ulcer or ulcerative colitis, applies also in otitis media. It is contraindicated, however, in acute otitis for the reasons outlined above.

Provided the drainage is thorough, nothing special need be done except to add Para-Spleen Co.*—1, q.i.d., or 2, t.i.d.—to the treatment. This is effective in a large percentage of the open cases, and it is not unusual for an old otitis media of years' standing to "soften up," discharge more freely, and heal in from six to eight weeks.

A Philadelphia otologist once told me that when he was at all fearful that the drainage in an old running ear was not the best, and especially when there was any infiltration around the eustachian tubes tending to close them, he always prescribed atropine to full physiological effect while he gave the Para-Spleen Co.

TINNITUS—Make it a rule to ask every patient with myxedema about ear noises, and the majority of them will admit that they have a more or less noticeable buzzing in the ears. Some myxedemics really suffer from this annoying condition, which may be as much a symptom of hypothyroidism as cracking noises in the joints, dryness of the skin, or the infiltration that is so often mentioned. In fact, I believe that some cases of aggravated tinnitus aurium are directly due to infiltration of the soft structures of the middle-ear.

Make it another rule routinely to find out what happens to the ear conditions of patients who are treated for hypothyroidism, and probably your statistics will agree with those already available, *i.e.*, that tinnitus, when accompanied with other evidences of hypothyroidism, often responds encouragingly to thyroid therapy.

VERTIGO—Simple vertigo may be produced by the same mechanical causes that are believed to be responsible for certain forms of deafness and tinnitus. Some interesting experiences have been recorded earlier in this chapter, so it must suffice here to say that simple vertigo accompanied with other indications of hypothyroidism has been completely controlled by the indicated organotherapy, and more than one such case had previously been diagnosed as Ménière's disease.

55. EPILEPSY

Epilepsy in Children—Thyroid Aspects—A Frequent Pituitary Factor—A Pituitary-Ovarian Complex—Ovarian Epilepsy—The Parathyroids and Convulsive States—Epilepsy a True Sympathetic Disease—Therapeutic Recommendations—A Question and an Answer.

MANY A medical mystery has come in for intensive study from the endocrine point of view simply because endocrinology has solved many a problem case.

Despite all the advances of the past few years, epilepsy still remains "the strangest of diseases," as Spratling once called it. We have by no means reached the ultimate in our knowledge of the etiology of this disease or of its treatment. The application of the ideas of those who have attempted to connect epilepsy with disordered endocrine function seems to be as worth while a way to progress as any other.

Much of the advance along this line has come as a result of empirical study. It has been said that the attempt to apply glandular therapy in epilepsy by the use of extracts of the pituitary gland, the thyroid, or the sex glands (alone or suitably associated) is subject to criticism; but to my mind such a procedure is better than the use of bromides, which, as we all know, are merely makeshifts.

There are still physicians who, when consulted by an epileptic, automatically write a prescription for "triple bromides, gr. xv, t.i.d." Whether this is a beneficial procedure or not, it certainly is not scientific. On the other hand, it is *known* that epilepsy is a nervous reaction to toxemia (much stress has rightly been laid upon the intoxication due to the usual hepatobiliary-enteric derangement so common in epileptics), and, of course, the ductless glands have much to do with the regulation of metabolism and detoxication. In fact, dyscrinism may be responsible for enough of the underlying conditions in epilepsy to make possible a revolution in its treatment and to enable us actually to cure the epileptic manifestations in a fair proportion of cases.

EPILEPSY IN CHILDREN—My own preoccupation with childhood endocrinopathies has brought me into contact with several hundred children with epilepsy. Many of these were already known to be endocrinopaths, and the epileptoid phase was merely an incident in a larger problem. Some of them had not been considered as endocrine cases before they came to me, and, in some, the endocrine stigmata were first noticed after they came under observation.

From all my experience, one important point emerges which I do not think will be gainsaid—epilepsy is very much more common in developmentally defective children than in normal ones. My first interest in the subject came as a result of the coincidental betterment of several cases of epilepsy in children who were receiving pluriglandular therapy for developmental dystrophies that were clearly of endocrine origin.

The fact that epilepsy commonly is found in the young, seems to indicate that something which takes place during the developmental period must be at fault. It is worth investigating whether or not some endocrine factor may be related to this, for it is in the young that the developmental processes are most active and that the endocrine glands which have to do with development render their most important service. It is during this period also that these all-important organs are most liable to show evidence of imperfect action.

It is well known that children who require special attention, who are backward, or in whom there is some developmental defect, as well as those who can be more definitely classed as endocrine, such as the cretins and Mongols, not infrequently have epilepsy also. Many of these have been treated with thyroid, and in some instances the betterment has extended considerably beyond the developmental feature, the epilepsy itself being improved. In many others, the combination of anterior pituitary, thyroid, and thymus (Antero-Pituitary Co.*) has shown an encouraging aggregate of results (46). The reduction in both the number and the severity of the attacks indicates that endocrine therapy is fully as advantageous in controlling this type of epilepsy as it is in modifying the associated endocrine irregularities that cause the developmental and mental defects. It is admitted that such a procedure is empirical; nevertheless, real progress has been made in the study and the treatment of epilepsy from this standpoint; and, best of all, many parents are rejoicing to-day over the marked improvement obtained in their children by this treatment.

After good results had been obtained with this method in children, it was quite natural to extend it to older persons. While the aggregate of results has not been nearly so good in adults, there has been some benefit in many cases—perhaps as many as 20 per cent.—and physicians have been encouraged to make a trial of this empirical form of treatment whenever they are confronted with epilepsy. There is enough clinical benefit to indicate the far-reaching results of endocrine impairment in epilepsy, and it is confidently believed that the consideration and treatment of this important factor offer the best hope of therapeutic success in many cases.

THYROID ASPECTS—Let us consider more closely the possible relations between "the chief endocrine gland"—the thyroid—and the epileptic background. It has been shown in many communications that disorders of the thyroid gland may be accompanied with epilepsy. In a paper published in 1916, entitled "The Relation of the Thyroid Gland to Epilepsy" (*Lancet-Clinic,* July 29, 1916, cxvi, p. 100), I collected a good deal of information which seemed to establish the belief that hypothyroidism is a predisposing factor in the cause of epilepsy, and that, when an epileptic has an associated hypothyroidism, treatment by the obvious organotherapy might have some beneficial influence upon the epilepsy as well as upon the thyroid condition. The conclusions drawn from this information are still fundamental:

1. Thyroid insufficiency is likely to be a frequent factor in the etiology of epilepsy for several reasons: (a) It favors toxemia; (b) it produces cellular infiltration and edema, which may directly affect the brain cells in the manner described by Hertoghe, Reed, and others; and (c) it usually causes other symptoms in epilepsy which have been definitely attributed to hypothyroidism.
2. Thyroid therapy is a rational therapeutic adjunct in the treatment of epilepsy accompanied with other signs of hypothyroidism.
3. Favorable results following the use of thyroid extract in certain cases of epilepsy should be considered as confirmation of these conclusions.

In recent years we have found an increasing interest in the water balance of the tissues in epilepsy and hints in writings on neurology in several countries which remind us of what Eugene Hertoghe, of Antwerp, taught forty years ago about cerebral infiltration, another name for the disturbance of the water balance of the cortex cells.

This is not the cause of epilepsy, for many a case of maximum infiltration that is obviously involving the brain, as shown by the extreme degrees of mental apathy and sluggishness associated with myxedema, have no symptoms comparable with epilepsy. But it seems to be a contributing or predisposing factor, which ought to be taken care of whether there is epilepsy or not.

A FREQUENT PITUITARY FACTOR—Nearly two hundred years ago, an observant Frenchman, Raymond Vieussens, noted pituitary disease at the autopsy of an old man who had long been a sufferer from epilepsy. Many a report since then has connected what has been called epilepsy with what has been called a pituitary syndrome. I do not believe that all cases thus labeled were true idiopathic epilepsy, nor do I think that the dyspituitarism was the sole endocrine factor present. But, despite our very obvious lack of knowledge regarding the cause, course, and cure of epilepsy, there is an increasing interest in the endocrine relations of epileptic manifestations.

Pituitary dystrophies have been connected with epilepsy by a number of writers. Several of the papers that show an evident relationship between dyspituitarism and epilepsy are doubly interesting because they include reports of good results following suitable organotherapy. The effort to modify this feature of the underlying dyscrinism has been of simultaneous benefit to the accompanying epilepsy. Just why the pituitary should be involved in the etiology of epilepsy does not seem to be very clear, save only as increased intracranial pressure from an enlarged gland might cause pressure on local structures which, in turn, might cause the typical attacks.

The condition called "pituitary goitre" (83) may be responsible for the unfortunately rare type of epilepsy that responds promptly and completely to pituitary therapy. This type of pituitary enlargement undoubtedly does occur, and its clinical explanation should be kept in mind.

I frequently have seen patients who confirmed the reality of the suggested relationship between the pituitary and epilepsy, which was discussed so interestingly by Harvey Cushing, of Harvard University, in his book, "The Pituitary Body and Its Disorders" (Philadelphia, J. B. Lippincott Co., 1912). Whether such a syndrome can be modified by organotherapy must always remain to be seen, for each individual is a law unto himself. At least, Cushing's points are as follows:

(1) Sir Victor Horsley, of London, noted increased excitability of the motor cortex in hypophysectomized dogs. (2) Epileptiform convulsions were frequently seen in animals that survived for long periods after partial removal of the pituitary. (3) Epilepsy is a frequent accompaniment of clinical conditions in which an insufficiency of the pituitary is manifest. (4) The pituitary may be damaged from a bursting fracture of the base of the skull. (5) It is believed that the posterior lobe secretion enters the spinal fluid, thereby bathing the cortex with a substance essential to the functional stability of the cortical cells. (6) Many individuals, supposed to be suffering from so-called genuine epilepsy, present symptoms of pituitary insufficiency, and, in some of these, pituitary extract has served to moderate the seizures.

A PITUITARY-OVARIAN COMPLEX—In an article entitled "Dyspituitarism and Epilepsy," by Hans Lisser and C. E. Nixon, of San Francisco (*Med. Clin. N. Amer.*, May, 1923, vi, p. 1471), the suggestion is made that there is a close connection between endocrine, especially pituitary, dysfunction and idiopathic epilepsy. Of the six cases reported, five had reached or passed puberty and "all presented menstrual disturbances especially characterized by a scanty flow and an abnormally prolonged interval." Mental retardation, particularly an impairment of the memory, was fairly marked in practically all the cases, and emotional disturbances common to dyscrinism were seen in

all. The interesting conclusion of these authors, as quoted in *Endocrinology* (Sept.-Nov., 1923, vii, p. 855) is:

"Organotherapy was administered to all six patients with strikingly beneficial results in the menstrual disturbances, obesity, and mental and emotional status. In the five patients under treatment for a long enough period of time, epileptic seizures either ceased entirely or became far less frequent and much milder. . . . The authors emphasize the importance of early apprehension and treatment of endocrine abnormalities."

Many experiences confirm this position. I have personally prescribed ovarian substance alone, anterior pituitary substance alone, thyroid substance alone, and various combinations of these three endocrines in at least sixty cases of epilepsy connected with dysovarism; and, while I have not had so satisfactory an average of results as Lisser and Nixon report, benefit was secured in more than half of these cases and an apparent cure in thirteen. When it is recalled that epilepsy is one of the most serious of the neurological problems and that just one attack is an experience through which no reader of this book would care to pass, any change that permits an individual who has had from two to ten attacks a day to go along with no further attacks at all, or perhaps with only one or two a month, is very correctly indicated as "nothing short of marvelous."

OVARIAN EPILEPSY—There is a type of epilepsy so closely related to ovarian functioning that it is more decidedly an ovarian problem than anything else. It is called "ovarian epilepsy" because the epileptic attacks, both grand mal and petit mal, are related either in the time of their onset or in the degree of their severity to the ovarian function—and particularly to ovarian dysfunction. In other words, certain women develop typical epilepsy, which on careful investigation is found to be connected with a pelvic difficulty, the attacks having been initiated in connection with some menstrual, obstetric, or postpartum experience. Further, a study of these cases by means of the diary and chart, indicates that the number of attacks and their severity have a wave-like character following closely the wave on the menstrual chart.

A number of suggestions have been voiced as to the actual cause of the difficulty. It is my opinion that the cause is not necessarily ovarian in origin, although clinical experience certainly connects the disordered endocrine function of dysovarism with ovarian epilepsy. Some writers believe that the pituitary gland is the principal factor and that irregularities in its size and activity come about as a result of the greater demands put upon it by ovarian functional irregularities, for it is well known that the pituitary plays an important rôle in the regulation of the ovarian service.

According to A. Souques, of Paris (*Presse méd.,* Feb. 7, 1931, xxxix, p. 185), menstruation and epilepsy are related under two conditions: when the attacks appear for the first time between puberty and the menopause, and when they recur during a variable length of time in synchronism with the menstrual periods or the times at which they should occur. In the first category menstruation and the crises coexist; in the second, the catamenia are absent, being replaced by epileptic seizures. Many cases reported in the literature and cited by Souques indicate that there is an actual, and not fortuitous, relationship between the two conditions, and that menstruation exerts a detrimental influence on the epilepsy. Further proof of this is afforded by the benefits resulting from ovarian therapy.

The pathogenesis of menstrual epilepsy is still unknown, but two theories of its causation are advanced: (1) that it is a reflex phenomenon, (2) that it is due to a humoral disturbance. Souques discusses these theories in relation to the physiology of menstruation, and suggests as the most probable cause the existence of a previous histological or biological alteration of the nervous centers together with an endocrine disturbance or an intoxication which, when a certain degree of concentration is reached, excites the cortex cells either directly or indirectly through the vagosympathetic system, thus causing the epileptic attack.

The thyroid has been considered to be an important etiological factor in some of these menstrual cases, largely because thyroid irregularities have often been uncovered in their study; however, the ovarian feature practically always appears to be equally important. As a matter of fact, the reader will quickly recall that of all the endocrine glands connected with ovarian functioning, the thyroid is among the most important. As Oliver T. Osborne, of Yale University, once said:

"The thyroid is typically a female gland, entering constantly into the woman's sexual life. Menstruation cannot properly occur without the activity of the thyroid."

THE PARATHYROIDS AND CONVULSIVE STATES—We have been convinced in a most incontrovertible fashion outlined elsewhere (81) that there is a connection between convulsive states like tetany, spasmophilia, chorea, etc., and hypoparathyroidism. The parathyroid hormone is a specific for the tetany of hypoparathyroidism, and there is an increasing suspicion that it has something to do with certain cases of epilepsy. A. Bisgaard, of Copenhagen (*Acta med. Scandin.,* Jan. 3, 1925, lxi, p. 433), connects parathyroid dysfunction with epilepsy, and states that administration of the parathyroid hormone benefits the patient. J. Madsen, of Copenhagen (*ibid.,* 1927, lxvi,

p. 536), asserts that Collip's parathyroid extract reduced the number of attacks and improved the psychic condition of three out of five epileptics.

Again, Edward A. Tracy, of the Forsyth Epileptic Clinic of Boston, from whose paper in *Clinical Medicine and Surgery* (June, 1931, xxxviii, p. 402) some points are quoted further on, says:

"It seems reasonably certain that certain vitamins whose absence results in nerve lesions may play a part in the prevention of epilepsy; and it has been shown that the tissues of persons having grand mal seizures are often deficient in calcium."

Tracy recommends parathyroid therapy (1/10 gr. with a glass of milk at meals) and, for the restlessness or severe motor symptoms, he advises calcium bromide from 10 to 40 gr. a day. It is certain that none of the forms of organotherapy used in epilepsy are sedative in effect, hence luminal or bromides are still in order. However, many an epileptic requiring 90 gr. of triple bromides a day has been able to taper this off and eventually to get along with no sedatives at all.

EPILEPSY A TRUE SYMPATHETIC DISEASE—Edward A. Tracy, who is the author of an excellent book on the subject ("The Basis of Epilepsy," Boston, R. G. Badger, 1930), believes that epilepsy is a progressive disease of the sympathetic neurons with evidences of a hypertonic condition of these fibers. This, of course, is a nutritional disorder in which there must be a very vital endocrine phase because of the close relationship between the endocrines and the sympathetic system. As Tracy says further (*loc. cit.*):

"There is an ample field for investigation as to what toxic substances or dietary deficiencies produce this hypertonia."

This investigation has been going on these many years, and, while it is no simple matter to put one's finger on some specific cause and say, "This is it," as our knowledge of the sympathetic-endocrine relations (4) increases we are confronted with many a clinical reminder that we are on the right track and that the endocrines are indeed vital in regulating these very factors. Tracy also finds satisfaction in the sympathetic sedative effect of the eclectic remedy, water hemlock (*Œnanthe crocata*), on the hypertonia referred to.

THERAPEUTIC RECOMMENDATIONS—There is no endocrine remedy for epilepsy, yet organotherapy has revolutionized our conceptions of what underlies this disease, and it has opened the door of hope to many a patient. Already we have found recommendations for thyroid, pituitary, ovarian, and parathyroid therapy; and it certainly is true that hepatic and hepatobiliary organotherapy, such as is outlined in Chapter 104, is often the best kind of fundamental treatment that one could advise—it is worth while in all forms

and degrees of epilepsy. Which shall we choose? My answer is, "Find the endocrine basis and then follow it as far as you can." It is possible to make fairly close differential diagnoses in endocrinology. A whole section (III) of this book is devoted to endocrine diagnosis.

Manifestly, "everything" should be done for the epileptic. Dietetic control (102), hepatobiliary detoxication (104), alkalinization (100), and alimentary stimulation—all are essential. Pluriglandular therapy is an adjuvant measure. So, in addition to the best care and advice, add organotherapy. Give it without hope of results. Promise nothing. It is effective only in endocrine cases, and can have no effect on an essentially organic disorder.

There are four endocrine measures most commonly used:

(1) The thyroid-detoxicating type, in which the idea of "liver wringing" (104) is supplemented with Endothyrin* in step-ladder doses—from ½ to 1 gr. a day for a week, doubling the dose each week for a month, waiting a week, then repeating the process. As in all cases of hypothyroidism, I always advise remineralization (100) with the organotherapy.

(2) The pituitary therapy—with the standard formula, Antero-Pituitary Co.*—based on the happy experiences in the treatment of defective children who also had epilepsy. This is started with 1 tablet q.i.d. (for adults) for two or three months. Later more pituitary is given, as outlined in the treatment of hypopituitarism (83).

(3) The treatment of dysovarism as a basic endocrine fault underlying menstrual or menopausal epilepsy. Here the treatment is that used in amenorrhea or the menopause. Since the pituitary-ovarian balance is shown to be especially involved, it is an advantage to use a thyro-pituitary-ovarian formula with a generous dose of pituitary or Gonad-Ovarian Co.* (80).

(4) Parathyroid therapy is indicated when there is evidence of hypoparathyroidism (81), especially a reduced blood-calcium index. Here it is sometimes well to alternate the second routine mentioned, *i.e.*, Antero-Pituitary Co., monthly with the parathyroid-spleen formula (Para-Spleen Co.,* 1, q.i.d. for two weeks then 2, t.i.d. for two weeks) that is used in hypocalcemia and spasmophilia.

A QUESTION AND AN ANSWER—The subjoined letter is worth quoting because of the pertinent question it contains and the excellent clinical report that is also included:

"That I am interested in your work, you already know. My experiences with your Antero-Pituitary Co. in a number of cases of epilepsy prompt me to ask this question: How can you determine in advance in which cases you may expect results from this treatment?

"You may be interested in the following recent experience: A man, at the age of twenty-eight, began to have epilepsy which for ten years gradually became worse in spite of treatment by a number of physicians. He had gone over the usual bromide road, and when I saw him a year ago, at the age of thirty-nine, he was having from five to eight heavy grand mal attacks daily. For a year now he has been taking Antero-Pituitary Co. After the first month's treatment the character of the attacks changed. After two and a half months my record reads, 'A few petit mal attacks daily.' Occasionally he would have a complete attack. Now he goes six weeks or two months without any seizure. He is not cured yet, but he is certainly a different man."

The answer made to this physician's inquiry may also be of some interest:

"Your experience was the more interesting because of the age of the man and the number and severity of his attacks. I know of no way definitely to determine in advance whether a given case of epilepsy is an endocrine one and likely to benefit from organotherapy or not. Naturally, if there are clear-cut signs of thyroid insufficiency or the appearance points to the pituitary, one would be justified in presuming that it might be an endocrine case. This, however, is no therapeutic criterion, for all such endocrine cases do not have epilepsy.

"While it is well to discover as many facts as possible about the endocrine side of a given case, this only supports the supposition that the case may respond to the treatment of the endocrine feature; it does not by any means establish it in advance. Frankly, while I am being surprised continually by the reports I hear of epileptics who have been treated successfully with organotherapy, I am equally discouraged about the very problem that you bring up. As things stand, we know very positively that many epileptics, chiefly the young, but also some older people, have been benefited by the use of this therapy. The attacks have been stopped entirely or their frequency remarkably reduced.

"We know that with the changes in the epileptic attacks there has often been benefit to other aspects as well, with a general increase in health and nutrition. True, these results have occurred in many hundreds of cases, but our figures do not allow us to determine the relation between results and failures; and, of course, of the latter there have been fully as many as the former.

"The frank answer to your inquiry is, 'There is no way to determine this in advance,' but I must say that I never see an epileptic without wanting to give him the benefit of the doubt and treat him from this standpoint. Even if we do fail after four or five months, we have done no worse than tens of thousands of other doctors have done with bromides."

In conclusion, there can be no denying the fact that treatment of this general character is neither inconvenient to the physician nor harmful to the patient; and, besides the very fair prospect for good results, it has an undoubted diagnostic value, which cannot be said of the bromides and other drugs commonly used in the treatment of epilepsy.

56. EYE DISORDERS

Adrenal Support in Asthenopia—Thyroid Therapy in Cataract—Parathyroid in Corneal Ulcer.

THE ENDOCRINES may influence the eyes in two ways, anatomically and physiologically. The anatomical changes in the eyes or the vision (squint and bitemporal hemianopsia) that accompany pituitary tumor are discussed as pituitary disorders (83). The other chief endocrine eye disorders are the exophthalmos and other ocular findings in Graves' disease, which are not intrinsically ophthalmic and so are discussed elsewhere (57).

ADRENAL SUPPORT IN ASTHENOPIA—There is, however, a matter pertaining to the ocular muscular tone that is quite important because its appreciation enables us to do something worth while in the endocrine therapy of asthenopia.

Some years ago an ophthalmologist was treating a man with hypoadrenia due to a postinfluenzal breakdown. The patient was being treated also by his regular physician, who very wisely was attempting to reestablish the depleted endocrine functions. The ophthalmologist noted that the asthenopia from which this patient was suffering improved simultaneously with the other hypoadrenal symptoms.

Later, another somewhat similar experience impressed upon this specialist the fact that the eye-muscle weakness of hypoadrenia responds to indicated adrenal support. Since then he has studied every case of asthenopia from the endocrine standpoint. Whenever he finds an exaggerated fatigue syndrome, low blood-pressure, and a history of experiences likely to have depleted the adrenals, he uses Adreno-Spermin Co.* with almost invariable success (35). And why should not the ocular muscle tone be subject to the same control that the rest of the muscles are subject to—from the standpoint of both etiology and therapy?

THYROID THERAPY IN CATARACT—Some very interesting clinical coincidences have aroused an interest in the thyroid aspects of cataract. Patients with varying degrees of hypothyroidism, who have been suffering from cataract as well, have in the course of the improvement from the needed thyroid therapy shown benefit to the opacity also.

Already there are a number of reports in the literature. For instance, H. Kirkpatrick, of the Indian Medical Service (*Brit. Med. Jour.*, March 25, 1922, i, p. 467), in a consideration of the etiology of primary cataract suggests that

"1. The cause of primary cataract is probably a constitutional one.

"2. Most of the morbid conditions which are associated with the development of primary cataract injuriously affect the action of the endocrine glands.

"3. Primary cataracts sometimes follow thyroid and parathyroid deficiencies, and are almost certainly then caused by a disturbance of endocrine function."

Kirkpatrick quotes Robert McCarrison, a fellow officer in the I. M. S. and a well-known student of thyroid disorders in India, as believing that

"the endocrine glands are injuriously affected by a deficiency of vitamins in the food, and that the harmful effect is likely to be enhanced if the diet is badly balanced and contains an excess of carbohydrates. This lack of essential food factors is frequently shown in India by the occurrence of beriberi, scorbutic conditions, and keratomalacia."

In this country, W. J. Kerr and his associates in the University of California (*Endocrinology,* March-April, 1926, x, p. 126) are convinced that various iodine compounds recommended for a number of years as suitable adjuvants in the treatment of cataract are valuable because of their effect through the thyroid gland. They report a number of cases of cataract actually treated with thyroid with both general and local improvement, and conclude:

"There is no great danger in the administration of thyroid substance, if the patients are carefully studied before treatment and watched for toxic symptoms. Improvement was noted in most of the cases benefited before any toxic symptoms appeared. The basal metabolic rate was within normal limits in practically every case, and in a few was toward the lower limit of normal. We do not feel that a normal metabolic rate contraindicates the use of thyroid medication, if it is carefully supervised. We have been using small doses of thyroid substance, for many years, as a general tonic, and have been pleased with its beneficial effects. In this we have felt that the action of the drug was probably similar to that obtained with small doses of iodides. . . . Other eye conditions have been treated with thyroid substance. In some cases of corneal ulcer, intractable to ordinary methods of treatment, the improvement has been prompt and striking."

A. Siegrist, director of the Berne (Switzerland) Ophthalmologic Clinic, has published a 400-page book on the causes and non-operative treatment of cataract (Berlin, Urban & Schwarzenberg, 1928). His own personal observations have led him to the conclusions that cataract in all probability should be attributed to endocrine disturbances and that the treatment should be pluriglandular. Siegrist observed thirty-two cases over a long period, and to these he gave a pluriglandular combination. There was improvement not only in the acuteness of the vision, but also in the objective, visible changes

in the lenses. On the other hand, when the treatment was discontinued, an aggravation or a reversion of the condition was noted. Siegrist expresses the opinion that the number of cases seen is far too small, and for this reason he challenges his colleagues to cooperate. Reports of this cooperation are not yet found in the literature.

A physician in San Antonio, Texas, who has had an interesting personal experience with cataract, writes the following:

"I am taking care of much referred work, especially looking after the constitutional side of eye disease. During the last seven or eight years some marvelous results have been obtained with organotherapy and antisyphilitic therapy combined, even regardless of a negative Wassermann. Remarkable cures have been effected in glaucoma, neurochoroiditis, neuroretinitis, cataract, and other diseases of the eye. I myself have been cured of double cataract by the use of 1/5-gr. thyroid tablets.

"Lately I have learned from a study of embryology how cataract responds to thyroid substance, just like myxedema—*the lens is modified skin.* From the ectoderm of the embryo, we know, come the skin and its accessories, the brain and nervous system, the pineal body, the posterior pituitary, part of the adrenals, and the organs of special sense. Practically all the eye structure, and of course, the lens, should be affected by thyroid treatment like the skin in myxedema. It is vital truth, and my own recovery has been very remarkable. I am doing more work with my eyes now than ever before in my life—reading, writing, microscopical work, and everything else."

Suggestion: To your usual treatment of these eye cases, add one or two tablets a day of Endothyrin.*

PARATHYROID IN CORNEAL ULCER—The nutrition of the ocular structures is under exactly the same cellular chemical control as the nutrition of any other part of the body. The quotation from Kerr's report (above) gives evidence of this. The healing of many old ulcers having been accomplished by the application of the ideas of H. W. C. Vines, of Cambridge (95), it occurred to some ophthalmologists who had seen or heard reports of ulcers responding to parathyroid therapy, to try the same treatment in ulceration of the cornea and the conjunctiva.

There is an increasing amount of evidence to support the claim that ulceration of the cornea responds to the calcium regulation made possible by Para-Spleen Co.* Although it is difficult to individualize the credit in a clinical way, I am informed that this method has been used with success even in the serpiginous type of corneal ulceration. The subjoined report suggests some interesting possibilities:

"The following case was diagnosed as trachoma and the usual treatment with silver nitrate, copper sulphate, etc., was carried out for a number of

years (at least nine). Finally, the case was rediagnosed as a badly treated case of follicular conjunctivitis. In view of the present interest in the use of parathyroid therapy in cases of ulceration, it was thought that perhaps parathyroid might be beneficial; so 1/10 gr. of Parathyroid Extract (P.D. & Co.) was given twice a day. After five days the patient returned, thoroughly frightened and with the conjunctiva bleeding. He was reassured that this was a good sign, and the bleeding stopped in less than twenty-four hours. Within the next ten days, the conjunctiva was clear for the first time in ten years, with the exception of the scars caused by previous caustic treatment."

The same physician later experimented with a case of corneal ulcer caused by infection with *Aspergillus albus*. Iodides by mouth and local argyrol eye washes continued for months, accomplishing nothing. When parathyroid was added to the treatment, however, there was a complete recovery within three weeks with only a slight corneal scar. As this writer says, "The parathyroid evidently stimulated repair in the ulcer." So parathyroid therapy is suggested as a part of the treatment of ulcerative conditions of the cornea and conjunctiva, just as it is recommended in ulceration encountered in otorhinological practice (54) and, in fact, in ulceration generally (95).

57. GOITRE

Classifications of Goitre—Endemic Goitre—Simple and Colloid Goitre—The Cause of Goitre in Girls—Exophthalmic Goitre—Toxic Goitre—Thyroid Adenoma—Transitional Types of Goitre—Thyroiditis—The Treatment of Goitre.

AN ENLARGEMENT of the thyroid gland is a goitre or a struma. It is functional and an advantageous defense reaction, or it is organic and a response to influences quite remote. It is surgical or non-surgical, depending often upon the point of view. It is the result of inherent pathology, *i.e.*, intrathyroid, or an incident in a much larger picture, or a combination of both of these.

The thyroid may be functionally inadequate or it may be overactive, and, unfortunately for the diagnostician, it may be both hypoactive and hyperactive. Its size has nothing to do with its function, for, as we shall see, some of the largest goitres are inactive and the worst types are perhaps the smallest.

Elsewhere there are discussions of hypothyroidism (67) and of hyperthyroidism (63). This division is made because of the extraordinary frequency of functional variations in the thyroid service with no sign of enlargement of the gland. The reader will do well to read these three chapters together, noting especially the discussion on terminology in the introduction to Chapter 63.

CLASSIFICATIONS OF GOITRE—H. S. Plummer, of the Mayo Foundation, classifies disease of the thyroid as: (1) diffuse colloid goitre, (2) adenomatous goitre without hyperthyroidism, (3) adenomatous goitre with hyperthyroidism, (4) exophthalmic goitre, (5) myxedema, (6) cretinism, (7) thyroiditis, (8) malignant disease, and (9) congenital thyroid anomalies. In virtually all of these there is enlargement of the thyroid gland.

Israel Bram, of Philadelphia, classifies goitre as surgical and non-surgical (*Amer. Med.*, March, 1931, xxxvii, p. 146). In the former category he includes (1) thyroid adenoma, (2) cystic goitre, and (3) fibrous goitre. In the non-surgical class he places (4) simple thyroid hypertrophy, (5) colloid goitre, and (6) "the hyperplastic thyroid swelling common to Graves' disease."

Then there is the classification (1) atoxic, (2) toxic, (3) malignant, and (4) inflammatory. This outline is effectively developed by S. L. Ledbetter, Jr., of Birmingham, Alabama (*South. Med. Jour.*, April, 1931, xxiv, p. 284), as follows:

I. Simple or Atoxic Goitres
- (1) Adolescent colloid
- (2) Adult colloid
- (3) Adenoma
  - (a) Fetal
  - (b) Single colloid } Solid or cystic
  - (c) Multiple colloid
  - (d) Malignant

II. Toxic Goitres
- (1) Primary hyperplasia, or exophthalmic goitre
- (2) Adenoma
- (3) Mixed, hyperplasia and adenoma

III. Malignancies
- (1) Carcinoma
- (2) Sarcoma

IV. Inflammations
- (1) Acute thyroiditis
- (2) Chronic thyroiditis
  - (a) Tuberculosis
  - (b) Syphilis.

ENDEMIC GOITRE—Enlargement of the thyroid with geographical incidence was the first of the several forms of goitre to be appreciated and studied, and many theories were propounded as to its cause. Pliny thought it was "mostly caused by the noxious quality of the water." Fourteen hundred years later (1530), Paracelsus considered the endemic nature of goitre in the Salzburg region and thought it was due to the mineral and metallic constituents in the water.

Robert McCarrison, in the British Indian Medical Service, studied the geographical incidence of goitre and made out a good case in favor of a water-borne infective cause. Doubtless the facts collated by McCarrison are incontrovertible, and infective causes do exist. But it remained for David Marine, in Ohio, to demonstrate conclusively that this form of goitre is dependent upon a lack of iodine in both food and water.

Once again the therapeutic test confirmed the diagnostic premises, and iodine therapy and prophylaxis have radically changed the statistics. It is now generally agreed that prophylactic treatment should be given to school children, especially girls, in all goitre areas. It is a vital measure also during pregnancy (84). Mass iodine therapy has not proved satisfactory, and iodized salt, so widely recommended, is criticized for the same reason—the dosage is not controlled nor is it varied with the individual. This subject is considered more fully in Chapter 103.

SIMPLE AND COLLOID GOITRE—Thyroid hypertrophy is commonly a defense reaction on the part of the gland. It is found in conditions of functional stress such as puberty and pregnancy. It may develop in any locality and while it is similar to endemic goitre (*q.v.*) in many respects, location is not connected with the cause. Heredity is an extremely important factor. Women who have symptoms of hypothyroidism during pregnancy undoubtedly transmit a tendency to thyroid defects to their offspring, especially their daughters. In fact, the prophylactic treatment of goitre, as well as other endocrinopathies, should start before birth! (84)

There are two forms of atoxic goitre: (1) the minor struma, in which there is a diffuse symmetrical enlargement of the thyroid, and (2) colloid goitre, in which the acini of the gland are distended by colloid material, causing a much greater increase in the size of the thyroid. The colloid goitre may grow quite rapidly, due probably to mechanical interference produced by the pressure of the swollen acini. This may be a cause of serious danger if the growth is substernal. The intrathoracic type of simple goitre should be treated surgically.

Nuclein, or sodium nucleate, has been recommended in simple goitre. By ten years' experience with its use, I have convinced myself that it improves the response to treatment with thyroid and iodine. These products are found in combination in Iodized Thyroid Co.,* which contains ¼ gr. each of thyroid, ferrous iodide, and nucleic acid.

THE CAUSE OF GOITRE IN GIRLS—Goitre is five times more frequent in girls than in boys, and it manifests itself particularly at puberty. I have a pet theory regarding its etiology: The thyroid gland is responsible for the initiation and maintenance of the ovarian function, and the anterior lobe of the pituitary assists it. (The reverse may be the case, but at least these two glands cooperate closely.) Now, the thyroid is also a very important factor in immunity as well as the leader in the regulation of the body chemistry. Suppose a girl at eleven or twelve has measles, scarlet fever, influenza, or some other acute infectious disease that puts an additional stress upon the immunizing service of the thyroid. Obviously the thyroid is more liable to fail in some of its other duties, especially if it happens already to be overburdened from a toxic standpoint—the girl doesn't eliminate well and has a tendency to acidosis. Particularly is this true if there is the additional handicap that makes goitre more common in certain localities.

In many instances I have traced the beginning of a goitre to some acute infectious stress that came at puberty when the thyroid had all it could stand without this added burden. Not only does this cause goitre, but it may be

the introduction to dysovarism or obesity, because the frequency with which thyroid enlargement occurs at puberty predicates a partnership with the ovaries, and because early thyroid dysfunction lays the foundation for endocrine problems in later life.

This point is emphasized in a very interesting way by A. E. Hertzler, of Kansas City (*Endocrinology,* March-April, 1926, x, p. 175). He cites a typical case of the young girl who has an enlarged gland, which is considered an innocent thing, and will in time disappear. That the girl is nervous and has dysmenorrhea is merely considered an unfortunate coincidence, but according to prevailing ideas the goitre is harmless. He then recites in familiar detail the development of the goitre through early married life and middle life—the result often being prolonged illness and an unnecessarily premature death.

This optimistic attitude toward adolescent goitre on the part of the profession is mentioned also by Anna S. Wilner, of New York (*Med. Jour. and Rec.,* Dec. 17, 1924, cxx, p. clxxxv):

"The thyroid is slightly larger in the female. It is frequently enlarged in girls at the time of puberty. Because of its occurrence at the time of life when the development is marked, the thyroid enlargement is spoken of as physiological. A careful study would show that this disposal of the subject is incorrect and most unfortunate. . . . The conditions that may cause this disturbance are manifold. . . . Suffice it to say that these unfavorable conditions are responsible in a great measure for the physical, emotional, and mental overstimulation that interferes with the metabolism and brings about a so-called toxic state, which, in its turn, causes an irritation and an enlargement of the thyroid."

The treatment of these patients should begin long before they come with the goitre or the obesity or the amenorrhea. My therapeutic deduction is a prophylactic one: Every girl at puberty who is forced by some infectious disease to submit to additional thyroid stress should be treated as though she already had a goitre. Iodine therapy may be of little value in controlling the acute infectious disease, but it should be a part of the treatment of all these cases. It is an advantage to give the equivalent of 1 cc. of Lugol's solution (each cubic centimeter of which contains 126 mg. of iodine) each week of indisposition, or 2 or 3 minims a day for two or three weeks.

When a girl who already has the beginnings of a goitre and perhaps some evidences of early ovarian irregularity is attacked by an acute infectious disease, there is a double reason for carrying out this "thyroid-sparing" procedure. In these circumstances it is an advantage to use small doses of thyroid extract itself either with, or instead of, the iodine.

EXOPHTHALMIC GOITRE—While, as we have seen (2), exophthalmic goitre was first described by a physician named Parry, in Bath, a more comprehensive and detailed consideration of the disease was published by Robert J. Graves, a Dublin physician, in 1835. Hence, in all English-speaking countries exophthalmic goitre is known as Graves' disease.

The definition given by W. M. Boothby ("Oxford Medicine," 1927, Vol. III, Part 2, p. 913) is:

Exophthalmic goitre is "a constitutional disease apparently due to an excessive, probably an abnormal, secretion of an enlarged thyroid gland showing pathologically diffuse, parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome and, usually, exophthalmos, with a tendency to gastro-intestinal crises of vomiting and diarrhea."

Several years after Graves' report, or in 1840, the German physician, C. A. Basedow, developed the subject still further and gave a comprehensive report of his experience. Hence, in the continental European countries the disease is commonly known as Basedow's disease.

The cardinal features of Graves' disease are: (1) loss of weight and strength—the patient tires with unusual facility; (2) tachycardia, at first manifest on the slightest exertion and later with no contributing cause; (3) excessive nervous irritability and tremor; (4) goitre, usually of a soft, round, and quite regular type—very different from the nodular, irregular adenoma of the thyroid (*q.v.*); (5) protrusion of the eyeballs, of varying degree, and other eye signs (31); and (6) a very considerable increase in the basal metabolic rate.

Israel Bram, of Philadelphia (*Am. Med.*, March, 1931, xxxvii, p. 146), makes some remarks that are both rational and convincing:

"The problem would be solved the sooner were there less confusion in the use of terms. While Graves' disease and exophthalmic goitre may be used synonymously, the terms toxic goitre and thyrotoxicosis are applicable solely to toxic adenoma. Toxic adenoma is a state of thyroid hypersecretion superimposed upon an old-standing simple adenoma. On the other hand, Graves' disease is a neuro-endocrine dysfunction characterized by an increased metabolic rate, loss in weight, tremor, emotionalism, constant afebrile heart-hurry, weakness, dermographia, and usually (not constantly) by hyperplasia of the thyroid gland and by exophthalmos. To state it briefly, in toxic adenoma it is the thyroid that makes the body sick; in exophthalmic goitre or Graves' disease it is the body that makes the thyroid sick. The implications in treatment, therefore, appear simple. In toxic adenoma it is the thyroid gland that requires major consideration in the form of thyroidectomy; in exophthalmic goitre or Graves' disease it is the individual possessing

the disease that requires major consideration, and when bodily processes are properly managed and corrected the hyperplastic thyroid undergoes spontaneous involution.

"This explains why surgery and Roentgenology so often fail in the management of these patients—it is, briefly, because they approach the problem from a local view-point. This, too, explains why the average general practitioner fails in his efforts to help his patient—it is because he looks upon treatment as a matter simply of hospitalization and the administration of iodine, a treatment which nearly always fails in its purpose. The solution of this problem will come about with the realization that this disease called exophthalmic goitre, more properly termed Graves' disease, must be regarded neither as goitre nor as hyperthyrodism, but as a constitutional affection."

There is much difference of opinion regarding the cause of Graves' disease. The German writer, Moebius, has long contended that hypersecretion of the thyroid gland is the essential cause of exophthalmic goitre. On the contrary, A. S. Warthin, of Ann Arbor, Michigan (*Ann. Int. Med.*, Dec., 1928, ii, p. 553), and W. M. Simpson, of Dayton, Ohio (*Am. Jour. Surg.*, July, 1929, vii, p. 22), both express the opinion that the thyroid gland is not the chief pathogenic factor but merely an incidental complication and sequel to some deeper constitutional disorder.

David Marine, of New York (*Am. Jour. Med Sc.*, Dec., 1930, clxxx, p. 767), remarks that, while the prevailing view is that exophthalmic goitre is essentially a thyroid disease, and while therapy should still be based on this assumption, he is convinced that a much more fundamental disturbance lies in a deficiency or derangement in the function of some other endocrine tissues, especially the adrenal cortex and the sex glands. He also believes that the principal manifestation in exophthalmic goitre is clearly a loss of control over the regulation of oxidation, as a result of which there is a physiological attempt toward compensation by increased thyroid function. In my estimation, the fact that thyroidectomy, while bringing about immediate and sometimes spectacular control of the physiologic responses to the excessive production of the thyroid hormone, often does not clear up the difficulty, confirms the position taken by those who believe that the thyroid in Graves' disease, at least, is the victim of circumstances elsewhere. On the other hand, in toxic thyroid adenoma there is a progressive intrathyroid change.

The treatment includes the control of every contributory cause, and, since these causes also produce hyperthyroidism, the subject is considered more fully under that heading (63).

Rest is the most important factor, and during this period of rest the most careful study of prospective causes should be made. The active treatment divides itself into two parts—radical and symptomatic. Radical treatment

consists of thyroidectomy, tying the thyroid vessels, or the use of X-rays, whereas the symptomatic treatment includes the regulation of endocrine imbalance involving particularly the ovaries and adrenal cortex, and the use of quinine and Lugol's solution. It is quite surprising how much symptomatic control is obtained by the use of Lugol's solution in many of these cases. Lugol's solution, the official compound of iodine (*liquor iodi compositus,* U.S.P.), contains iodine 5, potassium iodide 10, distilled water to make 100. The usual dosage is from 1 to 5 minims.

It was H. S. Plummer and his associates at the Mayo Clinic who, in 1922, reported the first attempt to treat a large number of cases of exophthalmic goitre with Lugol's solution (*Jour. Am. Med. Assn.,* June 30, 1923, lxxx, p. 1955). Later, results in the treatment of six hundred cases with this product were reported by H. S. Plummer and W. M. Boothby (*Illinois Med. Jour.,* Dec., 1924, xlvi, p. 401). They found the optimum dose to be 10 drops daily, although as much as 30 drops daily was given in severe cases. They estimate that two-thirds of these patients were greatly improved and one-fourth were slightly improved. Only one in twenty failed to show improvement.

Sedatives such as luminal or barbital are also frequently used, but it should be remembered that the influence of all drugs is symptomatic and not directed at the underlying fundamental difficulty.

One of the phases of exophthalmic goitre most difficult to control is the exophthalmos. Thyroidectomy or other measures that appear to give quite satisfactory symptomatic relief frequently have no effect whatever upon the exophthalmos. This phenomenon is now believed to be due to intraorbital edema resulting from mechanical obstruction of the venous return flow. H. C. Naffziger, of San Francisco, recently reported the removal of the supraorbital plate as a remedy for the intraocular tension associated with increasing exophthalmos. His reports claim complete relief.

TOXIC GOITRE—In the consideration of hyperthyroidism (63) the reader will see how and why I differentiate between hyperthyroidism and toxic goitre. Our concern here is with toxic goitre, sometimes known as thyrotoxicosis and other times called toxic adenoma of the thyroid.

What causes neoplasms? Many answer, "Cause unknown." Others say, "Local irritation," and still others include a factor of susceptibility that permits the irritation to cause the hypertrophic developments.

Toxic goitre is a thyroid neoplasm built upon a foundation of endocrine imbalance, toxemia of various origin, and heredity. The thyroid is hypertrophic, hyperemic, and functionally overactive. Its secretion is not only

increased in amount but it is perverted, its quality being changed almost more than its quantity. The goitre of Graves' disease is indeed a toxic goitre, but so is thyroid adenoma. Personally, I prefer not to use this term, though occasionally one encounters cases of unusually virulent toxemia that might be called "hypertoxic goitre."

THYROID ADENOMA—There is a very large literature about the pathology of the thyroid gland, but space here permits only the very briefest consideration of this subject.

There are two types of adenomas—those that cause no constitutional symptoms and those toxic adenomas that Plummer calls "hyperfunctioning adenomatous goitres." Thyroid adenoma differs from other forms of goitre in that the new growth is localized, round, and firm. Occasionally there are several masses making a nodular tumor. Both types ultimately require surgery —the inactive type, because of the danger of malignant degeneration; and the active type, because of the excess of perverted secretion which is so dangerous to the heart and nervous system.

TRANSITIONAL TYPES OF GOITRE—Among the several types of goitre that are misleading and misunderstood are (1) the thyroid instability of Léopold-Lévi, (2) the combination of colloid goitre and adenoma of the thyroid, and (3) what Frank H. Lahey, of Boston, calls "apathetic goitre."

The first of these is referred to elsewhere (67). The second is rare, and evidently is a secondary development of a new growth in an old colloid goitre—a simple goitre become complex. It occurs in older persons, and it may be possible by thyroid and iodine therapy to reduce the colloid part of the goitre thus making the adenoma more obvious. Of the third of these transitional types, Lahey says (*Bull. Chicago Med. Soc.*, Dec. 10, 1927):

"There is a type of goitre about which knowledge needs to be disseminated, that is, the apathetic type. There is a type of goitre that occurs in older people in which the activation is replaced by apathy; the type of older woman who is particularly bronzed. Pigmentation goes with this type. The eye signs are absent, the nervous signs are moderate, there is no excitation, the pulse is often low, from 100 to 110, the basal metabolism rate is low. This type is misleading because it is not a frank active type and the diagnosis is not made."

THYROIDITIS, which, fortunately, is not common, is an acute or chronic reaction to localized invasion by some organism, as in pyemia or syphilis.

The symptoms are what one would expect—pain, tenderness, enlargement. Usually there is hyperthyroidism. The treatment is expectant, with rest, local hydrotherapy, and, if necessary, drainage of the resultant abscess.

THE TREATMENT OF GOITRE—The chief difficulty in the successful treatment of goitre is due to the usual limitations of our diagnoses. There is a difference between the treatment of simple and colloid goitre depending upon the stage in which one finds it, its endocrine associations, and the other circumstances. The same is true of hyperplastic and adenomatous goitre.

First, *all cases* of goitre, no matter whether hypothyroid or hyperthyroid in nature, are considered from the standpoint of sparing the thyroid. In the former, various conditions are burdening an already played-out gland; while, in the latter, circumstances that may be identical are irritating a gland that is already frantic. So, detoxication is the first duty. The term should be much more inclusive than is usually supposed—for the toxins from foci of infection, from foods and other proteins to which the patient may be sensitive, from alimentary infections and infestations, all interfere seriously. As acidosis is practically always found in thyroid insufficiency and in most cases of hyperthyroidism, remineralization is in order (100). The liver frequently has broken down from overwork and is permitting protein-split products to pass its vital barrier. Obviously, if these substances get into the general circulation, the other emunctories must dispose of them; and the thyroid is an emunctory in that it regulates the emunctories. Hence, hepatobiliary stimulation (104) is often a most efficient supplementary measure.

As will be seen, iodine is an element inextricably related to the thyroid function and service (24). It is a specific remedy in certain cases of goitre, and it is astounding but true that iodine therapy renders a spectacular service in both extremes of thyroid dysfunction—endemic goitre and exophthalmic goitre. So important is this element that its value was suspected even as early as 1180, when the Salernitan physician, Roger, discovered that an unknown ingredient of seaweeds and sponges was useful in the treatment of goitre.

Further consideration of the treatment of goitre leads us to the study of the causes of the thyroid enlargement and the control of its results. This is considered under hypothyroidism (67) and hyperthyroidism (63).

In conclusion it must be stated that there is no single method of treatment for goitre as an entity, nor even for hypothyroidism or hyperthyroidism. One treats the patient, not the disease; hence goitre cures should be shunned, and all remedies directed at the thyroid used as a part of a comprehensive therapeutic procedure. Further, in view of the variability of thyroid function in different persons, at different times (of the month), and under different circumstances, no patient should be allowed to carry out an indicated line of treatment without close supervision. The best results always follow the most careful individual and persistent treatment.

58. GONAD DYSFUNCTION

Aspermia—Cryptorchidism—Eunuchism—Eunuchoidism—Hypergonadism—Hypogenitalism—Impotence—Presenility—Rational Treatment.

THE TERM "gonad" is used here in its most common sense, *i.e.*, to indicate the sex glands of the male. Attention is called to the important differences between the dysfunction caused by gonad changes and gonad dysfunction.

ASPERMIA—Male sterility, azoospermia, or aspermia is not an endocrine disease, although it is almost impossible for pathological changes involving the spermatogenic mechanism to develop in the testes without coincident interference with the endocrine sex regulating structures, the interstitial cells of Leydig. Aspermia is a result of atrophy of the spermatogenic cells or occlusion of the ducts. The most common causes are those that follow mumps (73) and any local damage.

It is frequently forgotten that it is possible for a man to be potent yet sterile, and this accounts for the improper diagnosis of sterility on the part of the wife in many cases. Every case of presumed sterility in the female should, from the start, be studied from the standpoint of aspermia.

When the male sex hormone was perfected (11) it was hoped that, because of its unusual potency, it would overcome certain cases of aspermia. It was used generously and persistently, yet without the slightest results on the aspermia.

There are writers who believe that persistent organotherapy directed at the pituitary and the thyroid may produce hypertrophy of small remnants of effective spermatogenic tissue, thereby replacing the destroyed structures with active secreting cells. Some reports indicate that this seems to have been done, but my own experience has not been encouraging.

The prospect for success with endocrine treatment is better in conditions that are sometimes confused with aspermia, in which immotile spermatozoa are produced. In these cases, the customary procedure recommended for the treatment of hypogonadism is indicated.

CRYPTORCHIDISM—Delayed descent of the testicles, unilateral or bilateral, is a moderately rare feature of endocrine interest. The stigmata of decided endocrinopathies need not be present, but practically always the boy with cryptorchidism shows other evidences of developmental defects of varying seriousness. In fact, cryptorchidism is usually found during the consideration of other manifestations that lead to the study of the endocrine aspects of the case.

It has been said that the testes cannot develop while they remain in the inguinal canal. If this is true, organotherapy is contraindicated until the gonads have been brought down by surgical means. Although I am not opposed to surgery, my experience has been that the effective treatment of an underlying endocrine dysfunction may cause the descent of these organs, thus obviating surgery. Hence, unless there is some good reason to the contrary, therapy is directed at the customary defects associated with developmental disorders in children (46). Antero-Pituitary Co.,* containing thyroid, thymus, and anterior pituitary, is particularly effective. It is my personal opinion that direct gonad organotherapy is contraindicated in children. Pluriglandular treatment given for six months—usually 1, t.i.d. for four out of every five weeks—has succeeded so many times that I never advise surgery until organotherapy has failed.

If, however, surgery eventually is resorted to and the disclosed gonads are ill-developed, it may be time to attempt—by means of pluriglandular therapy, as with Gonad Co.*—to hasten the developmental structural changes.

EUNUCHISM—The ancient practice of castrating slaves while they were yet boys produced the eunuch. Winfield S. Hall, of Chicago (*Med. Critic and Guide,* July, 1920, p. 220), gives this interesting description:

"These eunuchs of the Orient who were castrated before puberty may be described as flabby-muscled, squeaky-voiced, beardless, namby-pamby molly-coddles, whose temperament manifested qualities of cringing servitude and lack of initiative. There is a curious tendency on the part of these creatures to lay festoons of fat on chest and hips, presenting a pitiable similitude to the general outlines of the woman's body. These creatures are as different from a virile man as the gelding is different from the stallion. The secret of this difference is easily found in the fact that they have been deprived of the influences of the spermin from the testicles."

Loss of testicular activity through disease, such as mumps, produces an identical picture, the extent of which depends upon the amount of atrophy. It is impossible to control eunuchism, because it is the result of complete absence of testicular endocrine activity. Direct organotherapy of ultimate hypogonadism is virtually hopeless. There is but one thing that may be done for these unfortunates—treat the associated functional dyscrinisms.

The thyro-pituitary upset in eunuchs is responsible for many maximal symptoms. Replace a part of the missing gonad hormone, and the other glands are not so concerned about compensating for its absence. Homostimulate the depleted thyroid and pituitary, and there may be some real improvement. It all depends upon the extent of the loss and the capacity of these glands to respond to the proffered stimuli. Gland transplants, or mass injections of fresh emulsion, produce some results, but the benefit is fleeting.

EUNUCHOIDISM—The difference between a eunuch and a eunuchoid is one of degree only. The former has agonadism, the latter hypogonadism, in which the Leydig cells are partially but not completely lost. The condition is essentially that which follows mumps. It responds with fair satisfaction to the organotherapeutic routine suggested at the close of this chapter.

It should be stated that the prognosis of eunuchoidism, or of any other form of hypogonadism, for that matter, is not at all definite. Everything depends upon the responsiveness of the sound endocrine cells. The character of the cause of the damage and the age at which it occurs seem to make a great deal of difference. It is wise to attempt prophylactic therapy when, for any reason, testicular injury is foreseen, although accurate predictions are out of the question, for it is impossible to measure the extent of the damaging factors. Sometimes a severe case of mumps will cause little detriment, while a light attack will produce complete atrophy (73).

HYPERGONADISM—Sexual irritability is a fairly common clinical entity, but it is unlikely to be a real gonad problem. True gonad hyperfunction is caused by inflammatory or neoplastic changes in the gonads. Orchitis is not a direct endocrine difficulty—it is an infection. It may cause an endocrine syndrome, but it will be *hypo*gonadism. Hypersexualism may occur in conjunction with hyperpituitarism and, much more rarely, with hyperthyroidism.

Adrenal tumor, or hypernephroma (35), may be responsible for functional hypergonadism and the precocious puberty known as *pubertas præcox* (46). The prognosis is not good.

Erethism is most commonly produced by latent infections and mental causes. The treatment is not endocrine.

Seminal losses are practically never the result of intratesticular causes. Vesiculitis and posterior urethritis are more than likely the cause. Gonad therapy may aggravate these conditions.

The control of hypercrinism of any kind is usually much more difficult than the treatment of hypocrinism. The best measures are rest, general hygiene, and the discovery and control of the underlying cause.

HYPOGENITALISM—As the term "hypogenitalism" is ordinarily used, it designates a picture of hypogonadism and genital atrophy that is seen in the major forms of dyscrinism responsible for conditions of this kind. The rarer conditions—eunuchism and eunuchoidism—have been discussed already. Hypogenitalism is usually a pituitary disorder, although it may be caused by marked hypothyroidism. The functional aspects are responsive to suitable treatment, but the structural changes rarely respond.

Therapy is directed at the defective gonads and at the other endocrines believed to be responsible for the shortcomings. Pluriglandular therapy should be the rule, for one can never know which of the several probable factors predominates nor to what extent.

IMPOTENCE—The previous paragraphs have dealt with hypogonadism especially from the organic aspect. Now let us consider the more common every-day types of functional hypogonadism with their less ultimate yet just as disconcerting manifestations.

The causes of functional impotence may be divided into two classes—local and general. Among the former are (1) focal infections, specific and otherwise, and (2) functional excess. The results of these local causes are usually gonad in character. Thus the effects of sexual excess or a posterior urethritis are seen more in the gonads themselves than in the related endocrines. On the other hand, general causes, such as influenza, tuberculosis, or any other serious toxemia, affect the gonads only as a part of the organism as a whole. So in postinfluenzal impotence, for instance, the condition that has caused the gonad depletion *inevitably* has depleted the other glands. This distinction must be fully understood, for failure to recognize it has been a great stumbling-block to successful therapy, and has led to faulty conclusions regarding the efficacy of organotherapy.

Asexualism, which is usually an organic difficulty, must be classed with the conditions already considered. There is a common type of impotence in which the mental factors predominate; the fear of being deficient is the actual cause of the trouble. The victim may be temperamentally abnormal due to an educational aura, marital unbalance, or so-called religious convictions. In such cases organotherapy will show its limitations very soon, for it can neither regulate the habits of the patient nor change his mental attitude. Furthermore, if the condition reaches a state where a change is imperative, the point of view often overcomes the desire for treatment. As a rule, these patients do not cooperate well, and treatment usually is discontinued far too soon.

PRESENILITY is a term often misapplied to impotence and the depletion caused by hypocrinism. A man may be "old before his time" for many reasons, chief of which is sexual foolishness. Many cases of presenility respond spectacularly to organotherapy, but too often success is interfered with by lack of self-control, failure to discover and eradicate underlying causes, and an incomplete therapy—as regards both its pluriglandular character and its thoroughness and persistence.

Many a man fails to realize that old age is creeping on, and that with it there is a normal waning of gonad function. These men seek rejuvenation, but they often forget that no matter how effective treatment may be, they are much older after it is over than when they started. Senility and geriatrics are considered further in Chapter 88.

RATIONAL TREATMENT—The treatment of all forms of gonad dysfunction is the same, regardless of its name. Each of the enumerated disorders is a complicated problem, the complexity of which depends upon (1) the extent of the structural damage, (2) the length of time that has elapsed since the difficulty began, (3) the response of the other endocrines, and (4) the physiological resilience of these structures. It is a real problem not to be hurriedly considered and passed with a prescription for this product or that formula.

Then, too, there is the other difficulty that so often receives no attention at all—*the cause!* If hypogonadism is produced by a certain condition, circumstance, or disease, good judgment suggests—nay, demands—its discovery and control. Why expect endocrine therapy to control hypogonadism when the patient has latent lues? The treatment then should be antisyphilitic *and endocrine.* Why give endocrine therapy for impotence or asexualism while ignoring an old posterior urethritis? Why try "to beat the game" by feeding glands to a man who needs self-control or a different mental attitude? There is more to be said about this, but space forbids.

One more very vital point: Many cases of functional hypogonadism are the natural result of overstimulation—by alcohol, drugs, toxemias, infections, and hyperfunction. A necessary part of the treatment is the removal of all these stimuli, as well as coffee, easily putrefiable protein foods, the toxins of which a played-out liver is failing to dispose, and, I fear, tobacco! For this reason the aphrodisiac drugs are contraindicated—save only in the simplest cases—just as strychnine is contraindicated in hypoadrenia.

The treatment of hypogonadism must be comprehensive—never orchic substance, testicular transplants or injections, or organotherapy alone. The following routine is suggested:

1. Find the cause and treat it from the start.
2. Detoxication (99) and remineralization (100).
3. No stimulants—least of all aphrodisiacs.
4. Physiological rest—mental and physical—including the gonads also.
5. Endocrine therapy, always depending upon the individual case.

There are two ways to proceed in functional cases: If the cause is general, as an acute illness, the detriment will concern several structures. If it has

developed on a gonad basis, from a local infection or hyperfunction, and the health and condition are otherwise normal, the therapy is directed at the gonads themselves, unless or until the associated glands are also played out—then homostimulative organotherapy with the male sex hormone, Lydin* (11), will have to be supplemented with other endocrine synergists.

The philosophy of this pluriglandular treatment needs emphasis and explanation—emphasis because it is obviously better than testicular extracts, and explanation because of the several interesting, quite recent advances.

The suggested pluriglandular formula known as Gonad Co.* combines several products because there are several points of attack. What a writer once said about the female sex hormone is true also of the male sex hormone: "It cannot relieve symptoms due to a deficiency of some other endocrine hormone." This formula consists of:

1. Thyroid gr. 1/24 as a gentle reminder to the thyroid that it must maintain its full service. Many endocrinologists have found that a small dose of thyroid makes associated gland therapy more effective.

2. An active concentrate from the anterior lobe of the pituitary (the equivalent of 4 gr. of fresh material in each dose), because all the evidence shows that hypopituitarism causes hypogonadism, and the pituitary contains at least one principle that has been called "the motor" to the gonads.

3. An adrenal ingredient to serve as a muscular tonic.

4. Prostate extract (the equivalent of 9 gr. of fresh tissue) on the assumption that it cooperates with the Leydig cell functions, as explained elsewhere (20 and 85).

5. A gonad-stimulating concentrate from the interstitial cells of Leydig, to which two notable supplementary and cooperative principles have been added to form Lydin. As explained in Chapter 11, this last product is a combination of a physiologically standardized testicular active principle with the antisterility fat-soluble vitamin E, to which is added the new "anterior-pituitary-like gonad-stimulating hormone," as perfected by J. B. Collip, of the McGill University (19).

It is difficult to state a definite dosage. Gonad Co. is usually prescribed "2, q.i.d. at meals and at bedtime," but more than this may be taken. It is an advantage also to give several short series of intramuscular injections of Sol. Gonad Co.*—1 or 2 cc. daily for five doses, then every other day until five more injections have been given. This course may be repeated after a lapse of two weeks; the oral therapy is continuous. The treatment is given for at least six weeks, sometimes for much longer. In ultimate conditions like eunuchoidism, the minimum is six months.

59. HEADACHE

Adrenal Headache—Thyroid Headache—Hepatic Headache—Pituitary Headache—Ovarian Headache—Menopausal Headache.

SEVERAL TYPES of headache are of endocrine origin, and all of them are quite common. Although most of these are not treated as endocrine difficulties for quite some time after their appearance, fortunately the majority respond to the indicated organotherapy. This not only gives us therapeutic satisfaction but confirms in a very definite way the endocrine character of the difficulty. Incidentally, the idea of the therapeutic confirmation of endocrine diagnoses is one of the most heartening phases of endocrinology.

ADRENAL HEADACHE—There is no well-defined and identified type of adrenal headache similar to some of the other types of endocrine headache that are to be discussed here. But hypoadrenia is often accompanied by a dull, indefinable ache, comparable, shall we say, to the sensation one may feel when hungry and "all gone." There may be dizziness or not, depending upon the degree of hyposphyxia (35). The adrenal headache is a part of the circulatory insufficiency and hypotension usual in hypoadrenia. Increase the circulatory tone and raise the blood-pressure, and this symptom quickly disappears.

THYROID HEADACHE is extremely common, and differs from other types in that it cannot be located definitely. It usually is noticed in the morning upon arising, and wears off as the day proceeds. This characteristic is of definite diagnostic value, and is caused by thyroid inactivity, which has permitted the accumulation of poisons during sleep, and which ordinarily would be taken care of by normal endocrine activity. Thyroid headache sometimes is cured spectacularly by as little as ½ gr. of thyroid extract a day; but, when the headache is the result of infiltration of the actual brain cells, as in myxedema, larger doses must be given for a long time.

The successful treatment of endocrine headache predicates the discovery of the underlying dyscrinism and its regulation by means of organotherapy. Adreno-Spermin Co.* is very helpful in the chronic headache associated with run-down conditions; it also has a beneficial effect on the headache caused by defective circulatory tone. This formula contains sufficient thyroid for ordinary purposes, but not for well-advanced myxedema. When more thyroid is needed, it may be added in step-ladder dosage to determine tolerance: Give one ½-gr. tablet once a day for a week, 2 a day for a week, 3 a day for a week, 4 a day for a week; omit for a week or two and, if necessary, repeat the procedure.

HEPATIC HEADACHE—Another type of endocrine headache is due to defective hepatic detoxication and a breakdown in the capacity of the liver to destroy the protein-split products arising in, or coming from, the alimentary tract. When hypohepatism (66) occurs, the liver barrier to toxic substances is lowered, and the presence of wastes in the general circulation places an added burden on other organs, particularly the endocrine glands. One of the symptoms is a headache of indeterminate type that responds to measures designed to encourage the hepatic function (99 and 104).

The toxic or hepatic headache is best treated with hepatic stimulants. Where there is a clear-cut evidence of hypohepatism, as in essential hypertension, the hepatic detoxicating hormone, Anabolin,* is particularly effective. This remedy is especially helpful in the headache so uniformly present in hypertension and the preeclamptic states. In cases in which Anabolin has been beneficial and in which it is evident from the history that the liver has been acquiring its lazy physiologic habits for years, it is an advantage, after using this treatment for a few weeks, to change to Hepato-Splenic Co.* to overcome the tendency to revert to the former physiologic habitus.

PITUITARY HEADACHE—About the year 1913 I had occasion to analyze a number of cases of severe headache associated with menstrual irregularities, and came to the conclusion that the method I was then studying—that of Paul Dalché, of Paris, of broadening ovarian therapy by the addition of a suitable amount of thyroid—could be made still more effective by considering the possible pituitary aspects of this evidently pluriglandular disorder.

It is established that the pituitary gland, almost equally with the thyroid, is concerned in the initiation and maintenance of the sex functions.

From the study of several cases, it was evident that the pressure type of headache not unusual in cases with more serious menstrual irregularities might have a fundamental pituitary origin. In view of this, and because one occasionally finds other evidence of a pituitary defect in some of these cases, pituitary substance was added to the treatment. Thus ovarian therapy alone was first replaced with ovary plus thyroid, and later with ovary plus thyroid plus pituitary. The broadening of this particular form of organotherapy by the addition of pituitary substance is more noteworthy in those patients in whom the menstrual irregularity is accompanied with pituitary headache.

Because it is difficult to study conditions of this kind in the laboratory and comparatively easy to follow the more empirical clinical method, we had to presume that the added demands upon the pituitary during the period of ovarian difficulty caused a temporary hyperemia of this gland and a consequent pressure of the organ in its closely fitting sella turcica.

The clinical results that followed this form of pituitary therapy, and particularly those obtained by ovarian or thyro-ovarian therapy, prompted my conclusion that there is indeed a definite functional pituitary type of headache.

Some years later, Joseph L. Miller, the Chicago internist, prepared a paper on pituitary therapy as one of a series of propaganda articles on glandular therapy. In it ("Glandular Therapy," Chicago, American Medical Association, 1925, p. 61), he said:

"There has developed recently considerable literature on the value of pituitary substance by mouth in the treatment of pituitary headache. A review of the literature fails to reveal a headache that justifies this name, except in cases in which a tumor is present."

This statement could not have been based on any extended experience, for it was so contradictory to clinical experience. However, before then Irving H. Pardee, of the Neurological Institute of New York (*Arch. Int. Med.*, Feb. 15, 1919, xxiii, p. 174), had said:

"A disproportion between the pituitary body and the sella produces pressure on the sensory nerves to the dura; and by its encroachment on the cavernous sinuses it may cause interference with the cerebral circulation, the whole setting up the train of pituitary symptoms, including headache."

It is freely admitted that such disproportion might be caused by a tumor, but Pardee proceeds to give the clinical impression that such a headache produces:

"The headache is situated deep in the forehead behind the eyes. Deep pressure on the temples may elicit some tenderness. This headache is very persistent, usually lasting from half an hour to forty-eight hours, and it may be continuous, frequently coming on in the female at the time of the menses. . . . The administration of whole pituitary is specific . . . continuous medication with pituitary will result within a few days in a decrease in the intensity of the headache; there will be a longer period between their return. . . ."

Perhaps the most masterly article on the whole subject is that by William Engelbach and J. L. Tierney, of St. Louis, in Tice's "Practice of Medicine" (Hagerstown, Md., W. F. Prior Co., 1921, Vol. VIII, p. 405). A complete consideration of every feature of this disturbance is given and illustrated by clinical experiences. It is evident that these authors consider the pituitary gland the victim of circumstances that cause its undue enlargement, and that the pain comes about in the manner already outlined.

In the portion of this article referring to treatment (page 493), it is interesting to note the effect of therapy on some of the cases. One of these, a physician, age 31 years, was given simple thyroid therapy for the first

three months of her treatment. This had a beneficial influence upon one feature of the difficulty—she lost nearly 20 pounds in weight. The headaches occurred less frequently and were not so extremely painful, but the dysmenorrhea was not affected. Evidently the medication caused some symptoms of thyroidism, in consequence of which the treatment was interrupted for several days. Later, corpus luteum was added to the thyroid treatment for two months, but there was no further improvement in the condition. Then anterior pituitary was added to the thyroid and corpus luteum, and the treatment was given both orally and hypodermically. Soon the patient began to note marked improvement. After a month's treatment, "The patient had the first painless period in her menstrual life. The headaches, nausea, vomiting, nervous disturbances, mental confusion, and irritability have disappeared entirely." This pluriglandular treatment was continued for some time, "with remarkable freedom from symptoms and signs present previous to its administration."

This not only emphasizes the importance of oral pituitary therapy in dyspituitarism, especially in what I believe to be the compensatory, functional pituitary headache, but it shows the superiority of pluriglandular therapy in a most conclusive fashion.

The diagnosis of pituitary headache is based on three points: (1) the character of the headache—a splitting, rending pain; (2) its etiological associations and periodicity; and (3) response to pituitary therapy.

A headache caused by pituitary tumor (83) is seldom improved by any therapy except decompression or removal of intracranial pressure by spinal puncture. On the other hand, functional pituitary headache frequently responds promptly to the indicated treatment—particularly the regulation of dysovarism, as already suggested. An interesting case of more than ten years' standing comes to my attention as this chapter is being written. About six years ago a nurse in her late twenties consulted one of my associates, stating that since puberty she had had severe monthly headaches. The difficulty did not respond to any form of treatment and gradually became worse so that the patient suffered the most intense headaches, which sometimes lasted half of the month.

A diagnosis of pituitary headache was made and confirmed by a sellar radiograph—the clinoid processes were quite closely approximated, causing the pituitary to be squeezed.

For six years this woman has been taking Pituitary Co.*—equal parts of anterior lobe and total gland, each tablet representing about 14 gr. of fresh tissue—in doses ranging from 3 to 8 tablets a day, depending upon cir-

cumstances. It has completely controlled the headaches, and the report is that whenever her supplies ran out and she discontinued the treatment for a week or ten days, the headache would begin, and on starting the therapy again it would take almost a week to control it.

OVARIAN HEADACHE—The so-called ovarian headache is very often a combination of all three of the foregoing types, and is remedied by treatment that is capable of regulating the endocrine imbalance and the dysovarism—Thyro-Ovarian Co.,* for instance. The headache associated with the somewhat rare condition known as ovarian poisoning (80) is peculiarly resistant to treatment, and there is reason to suppose that it may be a form of protein sensitization, probably to an abnormal product of the ovarian stroma or corpus luteum. Ovarian therapy aggravates it.

The ovarian headache related to menstruation, varies greatly in different persons. In hypothyroid cases the headache usually is of the true thyroid type, in pituitary cases it is of the pure pituitary type. The ovarian demands happen to place the greatest stress where there is greatest weakness. There is a type of periodical discomfort called "menstrual migraine" by Neil C. Stevens, of Cornell University (*New England Jour. Med.,* Oct. 24, 1929, cci, p. 801). This headache is far different in degree, at least, from true migraine (72). Here is Stevens' excellent description, and special attention is called to his comments regarding the length of treatment:

"It comes on either before or after the period, sometimes both before and after. It is extremely punctual in the time of its appearance, the patient being able to foretell the day of onset exactly. The attack is usually severe and is nearly always associated with nausea and vomiting. Most women are unable to pursue their usual occupations and are forced to remain in bed a day or two. The headache lasts from six to twenty-four hours.

"Menstrual migraine is nearly always associated with a scanty menstrual flow. We have yet to notice this condition in a girl or woman where the flow was profuse. Many women are under the impression that their periods are normal when they flow three days and soil two or three napkins on the day they flow the most. For the examining physician merely to inquire whether the catamenia is normal is not enough. Menstrual migraine seems to bear some relation to dysmenorrhea, often appearing to be a substitute for it, although both conditions may occur in the same individual. Both, in all probability, depend upon an endocrine dysfunction and the consequent lack of development of the uterus.

"The writer of this article for a long time was extremely dubious of any treatment for this condition. Nothing but failure was recorded for several years. The reason for this failure was that the treatment was not sufficiently prolonged. Ovarian extract, including the whole gland, if given over a period of a year or two, will produce a marked amelioration in the symptoms.

Most patients take the gland for a month or two, and, not deriving an apparent benefit from it, discontinue it. But if one can get the cooperation of the patient and induce her to give it a year's trial, surprising results will be obtained. . . .

"In the course of two or three months after treatment has been instituted, there is usually cessation of nausea and vomiting; the pain is not diminished to any considerable degree. Then there will come a month when there is no attack of pain or vomiting, which fills the patient's mind with a false hope of cure. The following month she may have a severer attack than ever. But, gradually, periods unaccompanied by attacks become more frequent, until the old conditions are reversed and the majority of the menstrual periods are passed by with very little discomfort."

MENOPAUSAL HEADACHE—An indeterminate but very resistant type of headache is sometimes encountered in women between the ages of forty-five and fifty-five. This also is discussed interestingly by Stevens in the same article:

"It is more usual in those who formerly had migraine, although none of the peculiar characteristics of migraine remain. The headache is only occasionally severe. It is dull in character, occurring daily and lasting most of the day. The patient usually complains of it on arising. It is aggravated by worry and fatigue. The site of the pain may be frontal, occipital or upon the vertex. It is most commonly in the latter location. There is often more of a sense of pressure than of pain. In this group the headache is often not the prominent symptom, but one of many causing discomfort, a sense of inadequacy, nervousness, and fatigue.

"There are, at this period, two distinct groups in which headache occurs, the hypothyroid group and that group associated with the classical disturbances of the menopause. It is important to recognize this distinction as the treatment is diametrically opposite. The hypothyroid group is characterized by a dull headache, fatigue, lack of energy, subnormal temperature, low blood-pressure, slow pulse, dry skin, a sensitiveness to cold, and a low basal metabolism. The second group complains of hot flushes, nervousness, and headache. In this group, there has been no instance where the basal metabolism has been subnormal. For this type, ovarian extract acts almost as a specific, while thyroid or sometimes mixed glands act with almost equal success in the first. In the first group there is a tendency to anemia and the general condition is often benefited by the hypodermic injection of iron and arsenic. Luminal is often useful."

Practically all cases of endocrine headache are associated with demineralization, for the slowed cellular chemistry, which one expects in endocrine insufficiency, furthers the production of acid wastes that rob the body of its normal reserve of alkali. Consequently, the replacement of the alkali reserve is a reasonable associated treatment (100).

60. HEMORRHAGE

Epistaxis — Hemoptysis — Spontaneous Hemorrhage (Hemophilia) — Local Hemorrhage — Uterine Bleeding — Postpartum Hemorrhage.

THE SUSCEPTIBILITY to hemorrhage is a distinct diathesis varying in seriousness from nosebleed to hemophilia. The endocrine feature of these cases almost always involves the parathyroid glands.

The regulation of the blood calcium, as well as its effect upon the clotting time, is now definitely conceded to be a parathyroid matter. Therefore every type of hemorrhage must be considered from this standpoint, for, if the defect is a general one involving the blood calcium and it is considered only as a local one, obviously success will be limited.

EPISTAXIS—It does happen, however, that, when endocrine disorders in various persons have been controlled by suitable organotherapeutic intervention, there is often a coincidental improvement in a hemorrhagic feature. This has been particularly true in girls suffering from dysovarism and epistaxis, and in women with menopausal menorrhagia. Such patients were not considered from the "bleeder" point of view, treatment being directed merely at the dysovarism.

If the tendency to hemorrhage is associated with evident dyscrinism, treatment should always include an attempt to control the endocrine upset as well as the blood dyscrasia. In the earlier literature there are many reports of success as a coincident in the control of dyscrinism. For instance, R. Bernard (*Bull. et mém. Soc. méd. d. hôp. de Paris,* 1919, xliv, p. 702) outlines the clinical picture of a case of myxedema with epistaxis. As a result of the administration of desiccated thyroid, the coagulation time of the blood was reduced and the epistaxis was arrested. The author found accounts in the literature of twenty-three other cases of thyroid insufficiency with hemorrhages in which therapeutic success was complete. It is suggested that the thyroid may influence coagulation through its indirect relation to the calcium metabolism. My own hypothesis is that the usual cell toxicity of these maximal hypothyroid cases robs the body of alkalies, thereby putting added stress upon the parathyroids.

Nosebleed usually responds promptly to nasal tamponade with cotton soaked in adrenalin chloride solution 1 :1000, but such local treatment should always be followed by broader efforts to overcome the tendency, especially when it is discovered that there are some other evidences of endocrine imbalance.

HEMOPTYSIS—The majority of patients with hemoptysis have tuberculosis or some bronchopulmonary infection, in which the spitting of blood is caused by mechanical conditions. But, if a study is made of the blood calcium and the blood coagulation time in the chronic cases, frequently the former will be found to be low and the latter slow. Here parathyroid and spleen therapy may be utilized as a remineralizing agent and a means of modifying this phase of the difficulty. As the reader will see in Chapter 94, there are other prospects from calcium regulation.

For years the French have insisted that liver therapy is useful in hemoptysis, but it is not utilized in this country. This clinical service, however, is probably brought about by two influences: First, the well-known effect of liver therapy on the blood-picture appears to be caused by a direct influence on the blood production as well as on the other characteristics of the vital fluid, including its coagulability. From their experience in the treatment of more than 160 cases of pernicious anemia with daily feeding of adequate amounts of potent liver extract, G. R. Minot *et al.*, of Harvard (*Am. Jour. Med. Sc.*, May, 1928, clxxv, p. 599), conclude:

"Extracts containing the active principle effective in pernicious anemia, which acts specifically in small amounts, have simplified treatment. Treatment with potent extracts not only causes rapid blood regeneration, but appears to check the progress, or causes to vanish, certain signs and symptoms of the disease not directly related to the state of the blood or the blood-forming tissues."

On the other hand, any one who has studied the relations of hepatic function to the endocrine balance knows full well that defects in these hepatic detoxicative services immediately put a serious additional burden on the other endocrines, notably the parathyroids, as L. Morel, of Paris, has emphasized these many years. In fact, it is necessary to stress the relationships between the parathyroid and hepatic endocrine services for they cooperate very definitely with each other. Hence, just as needed parathyroid therapy may spare an overburdened thyroid or hepatic mechanism, so hepatic support may help materially in hypoparathyroidism.

There is some interesting experimental proof of this cooperative relationship in the work of O. O. Stoland, of the University of Kansas (*Am. Jour. Physiol.*, Feb., 1930, xcii, p. 35), to which attention may be called here. Liver extract (not the hemopoietic fraction, however) was injected into dogs suffering from parathyroid tetany, and "marked visceral reactions" were noted. These were accompanied by a temporary increase in the severity of the tetany, but this in turn was followed by a recovery from the tetany. In addition to this, there was marked fall in the blood-pressure following the

injections, so the statement was made that "our results indicate that liver extract may counteract the toxemia of parathyroid tetany."

The conclusion to be drawn from these findings is simply that the tendency to hemorrhage deserves treatment as a general condition chiefly by hematinic hepatic therapy, as well as by local measures, and doubly so when the customary measures—usually local—have been unsatisfactory. Such treatment is as valuable for its general and nutritive effects as it is as a hemostatic measure.

There are references to other endocrine measures in hemoptysis. For instance, fifteen years ago M. J. Konikow, of Boston (*Boston Med. and Surg. Jour.*, Sept. 30, 1915, clxxiii, p. 504), urged posterior pituitary as "a powerful hemostatic in pulmonary hemorrhages." Many good reports have been published since. A. Jacquelin, of Paris (*Monde méd.*, 1928, xxxviii, p. 689), prefers pituitary extract to emetine hydrochloride. He injects 1 cc. every two or three hours, later only once or twice daily. When the pulmonary hemorrhage is heavy, the intravenous route is advised, with from 1 to 1½ cc. well diluted with normal saline and given very slowly.

SPONTANEOUS HEMORRHAGE (HEMOPHILIA) — Hemophilia is an inherited or acquired blood disorder, characterized by a marked, abnormal tendency to hemorrhages, which frequently are uncontrollable. Whether this liability to bleeding is attributable to a specific or even a remote endocrine defect, cannot be stated definitely at the present time. Many investigators have shown that the delayed clotting time of the hemophilic blood is caused by a deficiency of thrombokinase in the red cells, which, according to Sajous, is a product of endocrine activity.

Hemophilia is usually an hereditary defect in the blood coagulability with a marked tendency to hemorrhage at slight provocation, which differs from purpura hemorrhagica in that the bleeding in hemophilia is not usually spontaneous, nor is there any modification of the blood-platelet count. Epistaxis may be the first sign of hemophilia or it may be brought on by a slight bruise, cut, or operation. It is a peculiar fact that hemophilia is virtually limited to the male, its incidence in females being very rare. The blood calcium is always low, sometimes extraordinarily so, but evidently this is but one of the blood derangements underlying hemophilia. Although hemophilia is rarely seen, its presence may be confirmed by a study of the blood coagulation time.

Rather striking clinical results have recently been reported in various types of bleeding following the administration of parathyroid extract, and experimental researches have shown that this substance raises the blood-

calcium level—for example, the report of B. Gordon and A. Cantarow, of Philadelphia, to which attention is called in Chapter 94. As a result of this relative or qualitative hypercalcemia, there occurs an increased viscosity of the blood. Frequently, it is not possible to detect an actual quantitative increase in the blood lime, but that there is a real increase in the amount of *available* calcium cannot be questioned. This availability of calcium is doubtless due to the ability of the parathyroid hormone to effect the ionization of a greater proportion of the calcium molecules in the blood-serum, thus hastening the formation of the clot.

We may now go one step farther: With the foregoing facts in mind, it was only reasonable to test parathyroid and calcium therapy in cases of hemophilia. Clinically, the results have been quite gratifying. Of the comparatively few reports available thus far, one may be summarized briefly:

Patient, R. T., a ten-months-old boy, with hemophilia. An elder brother had died two years before from the same malady. The usual classical symptoms of hemophilia presented themselves. The bleeding time was increased—in many instances to hours—and ecchymoses appeared following a pinch, a blow, etc., or even without provocation. Para-Spleen Co.* was prescribed, half a tablet crushed, with the food, q.i.d. In the course of a few weeks, unmistakable benefit was noted. The subcutaneous hemorrhages had become fewer and smaller, and a general physical improvement was apparent. The treatment was continued unabated for eight months. The child was then 17½ months of age; his color was good, and his health appeared to be perfect. The ecchymotic spots disappeared altogether, and scratches sufficient to cause bleeding lost their terror, for the blood coagulation is now as prompt as in healthy children.

There has been a renaissance in parathyroid therapy since the perfection of a physiologically standardized solution (16). A number of reports in the recent literature indicate that the value of parathyroid therapy in hemophilia is decisive, although in some cases the effects soon wear off. It is given by mouth or intramuscular injection, although some patients cannot even submit to a needle prick. In these cases a piece of fresh meat laid on the "wound" helps to stop the oozing. Products from various tissues like thromboplastin (brain) have a similar effect.

The relation of the liver to the production of blood and its characteristics has been appreciated for years, even though hemopoietic liver therapy did not come into accepted usage until 1927. The French have used liver extract as a hematinic for years, and several French writers attest its influence on blood coagulability. Referring to this, John Pickering, of London (*Lancet*, June 15, 1929, ccxvi, p. 1239), expresses the belief that hepatic activity is an important factor in the production of the essential participants in blood

coagulation. Three cases of typical hemophilia were treated with liver; there was marked improvement in the coagulability of the blood, although a normal condition was not attained.

In view of the peculiarities regarding the incidence of hemophilia in males, and because it is known that women carry the disease but are not subject to it, it occurred to Carroll L. Birch, of the University of Illinois (*Proc. Soc. Exper. Biol. and Med.*, April, 1931, xxviii, p. 752), to treat some cases on the supposition that there must be something in females that suppresses this tendency. Since the greatest physiological difference would be in the gonads, Birch gave injections of ovarian solution to a bleeder with real results, which lasted eleven months. Based on the same presumption, her colleague, H. B. Thomas, of Chicago, transplanted an ovary into the benefited bleeder's hemophiliac brother, causing a "cure" for five and a half months (until the graft was absorbed). This is a decidedly stimulating piece of clinical endocrine research which may radically change our conceptions of the subject.

LOCAL HEMORRHAGE—It would seem hardly necessary to explain here that organotherapy offers the most convenient and the most rapid means of controlling local hemorrhage. For thirty years adrenalin chloride solution in dilutions ranging from 1:1000 to 1:10,000 has been used as a local hemostatic. Its effect is caused by the startling vasoconstrictor effect of which it is capable, but it also may lessen the blood coagulation time.

Topical application of adrenalin solution by means of a spray or compress is well known. In hematemesis, from 30 to 60 minims of the standard 1:1000 solution is swallowed. In cystic hematuria, an ounce of a 1:10,000 solution may be injected into the bladder. In rectal hemorrhage or hemorrhoidal bleeding, injections or tampons of adrenalin solution, or suppositories containing the same principle with or without antiseptics or analgesics, are commonly used.

UTERINE BLEEDING—A distinction must be made between uterine hemorrhage and menstrual hemorrhage. There are pelvic hemorrhages related to utero-ovarian conditions that must be considered as such, *i.e.*, menopausal reactions or manifestations of ovarian dysfunction (80). Then there are hemorrhages of a more general character caused by diatheses or changes of a more constitutional nature.

It is somewhat difficult to differentiate between these, for both constitutional and pelvic causes are often so combined as to make an accurate diagnosis impossible. At least, we must consider uterine bleeding as a constitutional matter here.

Charles D. O'Keefe, of St. Louis (*Jour. Missouri State Med. Assn.*, Feb., 1931, xxviii, p. 64), discusses uterine hemorrhage, including both menorrhagia, or excessive menstrual bleeding, and metrorrhagia, or intermenstrual bleeding. He divides the causes into three groups: constitutional, local, and endocrine, of which the constitutional is of interest here.

Among the local causes, new growths, especially fibroma and carcinoma, are most important. Also, it is known that subacute appendicitis may become acute during menstruation because of increased congestion, which then will cause menorrhagia and dysmenorrhea. In course of time, when the disease has progressed sufficiently to impair the patient's general health and nutrition, the primary menorrhagia gives way to amenorrhea.

Among these constitutional causes, general acute infections are frequently at fault, especially if the onset comes at the menstrual time, intensifying the flow.

Constitutional conditions, such as diabetes, syphilis, nephritis with high blood-pressure, allergy, anemia, thrombocytopenic purpura, etc., frequently are responsible for menorrhagia or even metrorrhagia; and here again amenorrhea may result when the condition has become severe. Syphilis is a very important cause of menorrhagia, although it does not invariably increase the menstrual flow. In refractory cases of menorrhagia, O'Keefe considers it wise to order a Wassermann test, for, although these cases do not react to medication or curettement, they are promptly controlled by antiluetic treatment.

This author believes high blood-pressure to be a cause of uterine bleeding, especially in women past the menopause. He insists that even in normal pelvic findings a diagnostic curettage should be done to rule out carcinoma of the fundus before directing too much attention to the treatment of the hypertension. He issues a warning against the rather common tendency of subjecting these women to complete hysterectomy on the assumption of carcinoma or submucous myoma of the fundus. These patients are poor operative risks, and surgical treatment should be undertaken only after a positive diagnosis of cancer has been made.

In some cases, uterine hemorrhage may be due to nervous conditions. The vasomotor nerves of the pelvis are connected so intimately with the psychic centers that pelvic stimulation may follow marked emotional changes. O'Keefe quotes Emil Novak, of Baltimore, who reported the case of a woman with a history of normal menstruation who was frightened when the Christmas tree in her home caught fire, and a hemorrhage resulted which lasted from six to eight hours. Sometimes menstruation is affected through nervous

unrest because of fear of pregnancy. In such cases, especially in young girls who have been indiscreet, the following menstruation may be delayed a few days and then a profuse flow occurs. This menorrhagia may be explained entirely by removed inhibitions on the vasomotor nerves of the pelvis controlled through the psychic centers.

Hypoparathyroidism, hyperactivity of the anterior lobe of the pituitary, and hypoactivity of the posterior lobe theoretically should cause an increased amount of the uterine flow. The difficult diagnosis causes the treatment to be empirical. O'Keefe has controlled uterine hemorrhage with parathyroid tablets and active parathyroid solutions intramuscularly. Removal of pituitary tumors arising from the anterior lobe has been known to help control uterine hemorrhage. Many physicians have controlled uterine bleeding by the use of posterior pituitary products, although this does not prove a deficiency in the posterior lobe.

E. Allen and H. C. Goldthorpe, of Chicago (*Am. Jour. Obst. and Gynec.*, March, 1929, xvii, p. 344), state that for two years they have administered parathyroid for the control of excessive menstrual bleeding. In a series of fourteen young girls who complained of severe menorrhagia, they obtained good results in five, fair in six, and poor in three. All of these patients had been treated unsuccessfully with various hemostatic procedures, a number of oxytocics, the injection of foreign proteins, and also with surgery. The optimum dosage seemed to be about 40 units of Parathormone given intramuscularly each day for five days. Most effective results were obtained by combining this medication with a daily dose of from 120 to 180 gr. of calcium carbonate or lactate by mouth.

POSTPARTUM HEMORRHAGE—There are three outstanding causes of hemorrhage following delivery: (1) mechanical interference, (2) subinvolution, and (3) hypocalcemia. Sepsis is another matter entirely. Two of these factors are susceptible to endocrine therapy, and in many instances it will clear up the difficulty very satisfactorily.

First, it must be said that the proper obstetrical organotherapy with posterior pituitary, or preferably Pituthymin* (page 172), not only intervenes effectively in the actual process of delivery, but hemorrhage is unusual following its use.

In the consideration of subinvolution (96), stress has been laid on nursing as a physiological factor in preventing delay in the normal uterine involution. It is remedial in postpartum oozing also, and hence galactagogue organotherapy is as beneficial in the control of subinvolution as it is in postpartum hemorrhage.

There are many reports in the literature on the value of mammary therapy as a uterine decongestant. It is also a galactagogue. The tonic effect that placenta therapy exerts on the uterus is less well known, but nevertheless very real. There are many who insist that total pituitary gives both a uterotonic and a galactagogue effect. A combination of these three essentially postpartum remedies, as found in the formula, Placento-Mammary Co.,* is indicated in postpartum hemorrhage provided it is associated with subinvolution. Give large doses from the start—2 or 3 tablets three or four times a day for the first few days, reducing this to 2, t.i.d. for the first two or three weeks, and to half this for several weeks thereafter, depending upon the milk supply. (See Agalactia—70.) Liquor Pituitarii serves as a uterine hemostatic in emergencies, but before it is given—1 cc. (10 international units) every two or three hours—one must be sure that the uterus is empty.

If the patient is poorly nourished, of a tuberculous type, or known to have a history of either lime starvation or a tendency to bleeding, it is justifiable to presume that the blood coagulability may have something to do with the bleeding from the uterus. Here a few injections of Paracalcin* plus oral therapy with Para-Spleen Co.* will render three desirable services: increase the available blood calcium, raise the coagulability of the blood, and exert the healing effect that has made this measure so dependable in the treatment of general ulceration.

61. HODGKIN'S DISEASE

THE PROGRESSIVE enlargement of the lymphatic glands, the involvement of the spleen, and the ultimate anemia and cachexia which together make the picture described in 1832 by Thomas Hodgkin, of Tottenham, England, have led to an intensive effort to identify this condition as an actual endocrinopathy, or the direct result of one.

Many inquiries have come to me asking if there is not something in endocrine therapy that could be used with some hope of benefit in Hodgkin's disease. The fact that this condition involves the lymphatic glands in a very noticeable way has led to the belief that glandular therapy might be of service. But, unfortunately, it is not.

The origin of this disease has been attributed to tuberculosis, syphilis, and other infections in turn. As long as the etiology is not known, treatment must be empirical.

The spleen and the lymphatic glands themselves have been considered as sources of remedies calculated to spare the overburdened lymphatic system, and there are a number of hints in the literature that such measures have appeared to be helpful. But Hodgkin's disease evidently is beyond our present organotherapeutic horizon. Attempt after attempt has been made to incriminate every one of the endocrines. Hundreds of cases have been studied from the special points of view that enable us to identify particular types of dyscrinism. The metabolism varies, but in no decisive fashion. The blood findings are wrong enough, especially the white count, but the blood sugar and blood calcium usually are unchanged; the pancreas and parathyroids are apparently normal. There are indeed asthenia and several signs of adrenal insufficiency that are found in cachexia. Hence the suggestion to try adrenal support is not unreasonable, especially when pigmentation is noted occasionally in patches and sometimes as a more diffuse bronzing. But adrenal therapy helps little, and, despite symptomatic benefit, the progress of the disease is not stayed. The pituitary has been suggested, but attempts to utilize its marked regulating influences have been unsuccessful. There is no chance to incriminate the ovaries, for Hodgkin's disease is more common in men and, when it does occur in women, it has no special relation to puberty, menstruation, or the menopause. So we must give what little hope we can by ordering treatment with the X-ray and, perhaps, radium.

Hodgkin's disease frequently includes a syndrome involving the endocrines. If there is evidence of adrenal disease, for example, it is proper to attempt to modify it with suitable organotherapy while other measures are directed at the other features of the problem.

62. HYPERIDROSIS

THE INFLUENCE of mental and physical conditions upon the perspiration is very well known. The cold sweat of fear and the night sweats of tuberculosis are only two among many illustrations. One of the peculiarities of thyroid disease has to do with the activity of the sweat glands. In hypothyroidism, the skin is dry and rough, and the sweat glands are inactive; while in hyperthyroidism the opposite is the case, the skin being warm and moist and perspiring easily.

Hyperidrosis, as I understand it, is not just an increase in the perspiration, but is a serious form of excessive sweating in which, as has been said, "the sweat glands have gone mad." My interest in this subject was especially stimulated by a clinical case—a young man who perspired in a degree far beyond anything that I had supposed was possible. Water streamed off him constantly. Standing stripped in my office, the water dripped off his fingers, trickled from his armpits and down his back, and his face appeared as though he had just finished some excessive muscular activity, when, as a matter of fact, he had been resting quietly in the waiting-room for more than half an hour.

Naturally in extreme circumstances like this, the patient is most uncomfortable and a nuisance to all those who have dealings with him. Besides this, he is especially subject to colds, pneumonia, etc.

Not knowing what else to do, I considered this case as one of excessive sympathetic irritability, very much as we find in hyperthyroidism, but no marked evidence of thyroid hyperfunction was found. The treatment given, however, was that for hyperthyroidism. Crotti's formula (page 464) was given for its expected sympathicosedative effect, and, to the astonishment of all of us, this most difficult situation was quite promptly controlled. The young man said that he felt really dry for the first time in years, except immediately after drying himself after a bath.

With regard to the night sweats of tuberculosis, the general weakening effect and the increased susceptibility to colds due to chilling are indeed very important, and every effort should be made to control this distressing condition. Here, again, this same treatment has been used with advantage, although, having had some satisfaction in early practice with agaricin as a remedy for night sweats, I always prescribe it also. It is certainly true, as the reader will see in the consideration of tuberculosis (94), that in this disease the principal units of the endocrine system almost invariably have been seriously upset and the resulting endocrino-sympathetic conditions cry out for treatment.

63. HYPERTHYROIDISM

Terminology—Hyperthyroidism Is Thyroid Irritability—The Picture of Hyperthyroidism—Differential Diagnosis—The Treatment of Hyperthyroidism—Endocrine Sympathetic Sedation.

ALREADY UNDER the heading of goitre we have briefly discussed three forms of thyroid enlargement of which hyperthyroidism is a symptom—exophthalmic goitre, toxic goitre, and thyroiditis (57). To distinguish between conditions usually included under the blanket description of hyperthyroidism, we must first define our terms.

TERMINOLOGY—*Hyperthyroidism* is a term intended to denote a condition dependent upon or related to an excessive functional activity of the thyroid gland. It does not necessarily mean exophthalmic goitre—though it is a fundamental part of this disease—neither does it indicate solely the serious thyrotoxic cases that we occasionally see.

There are several other names frequently used to indicate this disorder, and they should be mentioned here if only to show why they are not used instead of the term that is to be used exclusively in these pages. The syndrome first discussed by Jacob Parry, of Bath, England, as far back as 1786, is now connected with hyperthyroidism; but hyperthyroidism is not necessarily Parry's disease. Nor is it the syndrome of Graves or of Basedow, which, in this country at least, is most often called exophthalmic goitre. This latter is an individual, constitutional disease in which hyperthyroidism is a part of the syndrome together with exophthalmos and a diffuse, parenchymatous goitre and a fairly uniform nervous syndrome that includes sympathicotonia, temperamental instability, tremor, etc. Hyperthyroidism is present in exophthalmic goitre, but it must be emphasized that many hundreds of cases of hyperthyroidism show neither exophthalmos nor goitre. As a matter of fact, enlargement of the thyroid occurs in only one-fourth of all cases of hyperthyroidism, and ocular protrusion in a still smaller fraction. Hyperthyroidism is a fundamental endocrine metabolic disorder, of which exophthalmos and the goitre may be clinical results, the latter showing itself earlier and more routinely, and the former being found only in certain cases.

Dysthyroidism, a quite commonly used term, was intended by many early writers to mean hyperthyroidism. To my mind, this name is not advisable, for dysthyroidism means perverted thyroid function or dysfunction of the thyroid, and naturally this should include hypothyroidism, the *instabilité thyroïdienne* of Léopold-Lévi, and, of course, hyperthyroidism.

Basedowified goitre is a term occasionally seen, especially in the continental literature, where the German name still clings to this disease. By it is meant a simple goitre that has developed a train of hyperthyroid symptoms—a superimposed Basedow's syndrome.

Thyrotoxicosis is certainly applicable to serious cases of hyperthyroidism, but it has come to indicate chiefly the maximal form of thyroid intoxication and is more often connected with the exact disease picture known as toxic adenoma of the thyroid than with the condition we think of as hyperthyroidism. Adenomata, or real neoplastic growths of the thyroid, usually cause symptoms of hyperthyroidism, but the pathology is different. Indeed, one of the great errors in the finer diagnostics of dysthyroidism is the mistaking of a simple enlargement or hyperplasia of the thyroid, in the presence of hyperthyroid symptoms, for an essential tumor. Often it is removed, only to find that the thyroid has been the victim of extraneous offenders that have been ignored and are still irritating the remaining gland tissue and causing a repetition of the same trouble.

Toxic goitre may also mean both of the previously mentioned conditions, and, in my opinion, should be eliminated, for an adenoma and an abnormally irritated thyroid are both sources of toxemia with very different pathology.

Some authors claim that all these diseases are different degrees of the same thing. I differ, though I admit that hyperthyroidism may develop into thyrotoxicosis, and that toxic goitre and thyroid adenoma may become very similar. But hyperthyroidism may also develop into myxedema, though this is rare, there more commonly occurring a peculiar complex that Léopold-Lévi, of Paris, called *l'instabilité thyroïdienne.* When the patient comes for consideration, her case may be definitely diagnosed as hyperthyroidism with a high B.M.R., but before the preliminaries are over, say in a week or ten days, she may be found to have a picture of hypothyroidism with a low B.M.R., slow pulse, and several of the expected findings of thyroid insufficiency. This is the characteristic instability of the thyroid.

Thyroidism is sometimes improperly used for hyperthyroidism, when in reality it indicates the conditions resulting from overdoses of thyroid extract or thyroxin, and is not a real disease.

This is all very disconcerting, the more so when the therapeutic consensus is so varied. I differ with some authorities in believing that hyperthyroidism is not a definite disease of the thyroid with varying degrees of severity. The difference between the disorders generally classed as examples of hyperthyroidism is not so much in degree as in origin. Sometimes the mischief comes from within, more often from without. In other words, thyroid disturbances

are nearly always effects of disturbances elsewhere; and, while different extraneous irritations may produce similar clinical effects, these effects are different diseases etiologically and therefore therapeutically. Only as we appreciate this shall we diagnose with intelligence and treat with success. The thyroid occupies much the same position among glands as the stomach does among the viscera. He is a hired mourner who weeps for others' ills besides his own—often for ills far removed from his own family of glands. Sometimes his sorrowings are loud enough to confuse our judgment, and we give our attention to him instead of to the real sufferer.

HYPERTHYROIDISM IS THYROID IRRITABILITY—In view of the seriousness of hyperthyroidism and the really great amount of misunderstanding about it, it seemed best to give additional consideration to the problem as an entity rather than as a feature of several serious thyroid diseases. So our consideration here is not of Graves' disease nor of thyroid adenoma, but of *thyroid irritability*.

The thyroid gland is stimulated by several kinds of circumstances—toxemia of varied types and degrees, undue emotional stress, the complications of sympathetic irritation, fatigue poisons, etc. But there are innumerable persons whose thyroids withstand many such toxic and irritating conditions, which in other people upset the gland in a most disheartening way. The difference lies in the physiologic substratum. The hypersusceptibility of some individuals may be attributed to heredity, prolonged stress, and certain predisposing geographical conditions. Sex has much to do with the susceptibility, for statistics show that 80 per cent. of the recorded cases of hyperthyroidism are in women—usually young women.

To rephrase an idea already stressed, the thyroid is quite as often sinned against as sinning. Hyperthyroidism is a reaction to any spur that goads the thyroid gland to increased functional activity. The usual causes of such irritation are emotional or psychic, infective or bacterial, toxic or chemical, and dyscrinism elsewhere. If the thyroid is forced to submit to the irritating stimuli due to a focus of infection, an alimentary infestation, or a protein sensitization, *what happens after the thyroidectomy?*

The best prospects for success in the treatment of hyperthyroidism depend upon an early discovery of the thyroid involvement and the uncovering of the underlying cause; for, if this cause is not identified and controlled, what is to prevent it from continuing its detrimental influences after most of the offended (not so much offending) thyroid has been removed? Herein is the really difficult problem—the treatment of the patient *after* thyroidectomy! The operation is seldom performed for reasons inherent in the thyroid

itself—the heart developments are the problems that call for speed and action. But, if the thyroid is sacrificed as an innocent victim to the surgeon's misunderstanding, the last error may be infinitely worse than the first.

If we concede that the thyroid is usually the victim of circumstances, then the proper treatment of hyperthyroidism *must* include the discovery and control of these circumstances—and this is not always done before the surgical intervention.

THE PICTURE OF HYPERTHYROIDISM—This chapter is a consideration of the fundamental basis of hyperthyroidism, a study of thyroid irritability from a medico-diagnostic-prophylactic standpoint. It is not a consideration of thyroid adenoma or goitre heart, which are ultimate and, I freely admit, surgical problems. In such cases, the thyroid is the aggressive sinner that must be curbed—and that promptly. Our subject is suffering from neither of these diseases, but is a nervous, irritable, supersensitive soul who has gone through some recent stress, and finds that she cannot slow down. She is physiologically plus—all functions seem to be speeded up. She thinks too much, and can't stop at bedtime. She perspires much under the slightest provocation. She is very sensitive to external impressions of every description—emotional, psychic, sexual, and toxic.

What previously was tolerable and acceptable, now becomes intense and perturbing; and, because of this intensification, these patients are soon depleted by the overstimulation. The circulatory responses are peculiarly marked—they blush easily, they are alternately hot and cold, the cardiac responses to the customary stimuli are increased and prolonged; they have heart-hurry and heart pains; in short, they are heart conscious. From a gonad aspect, erethism is not uncommon, with either emissions or menorrhagia; there is sexual instability with upsets based thereon.

Altogether the picture is one of hair-trigger activity and fierce unrest, a syndrome that keeps the patient in a perpetual stew. These persons can neither rest well at night nor relax well during the day. They cerebrate at an amazing rate—hyperthyroidism is said seriously to be a concomitant of genius.

And to all these signs and symptoms we can add several clinical findings that sometimes are ignored until the patient is seriously ill: gastro-intestinal instability with alternating constipation and diarrhea; tachycardia and cardiac irregularity; loss in weight and strength; and a considerable increase in the basal metabolic rate. To all intents and purposes these patients have Graves' syndrome, yet they may have no goitre, no exophthalmos, and no tremor—these may come later.

The picture may not have been completely painted here, but every experienced reader can recall a recent illustration or two of this very syndrome, for it is far too common.

What shall we do for patients in this category? The answer cannot be put into a nutshell, for hyperthyroidism involves as many problems as there are kinds of people—and they differ so very greatly.

First, we must appreciate the causes, which, unfortunately, seldom come singly. It is useless to decide that the hyperthyroidism is the result of, say, infected tonsils or subdental abscess, which, being removed, leave the patient to get well. We must be sure that the patient has no other foci of infection that have been overlooked. It is very easy to find an etiological alibi and, having done so, to consider that our diagnostic search is over. We must test the protein sensitiveness of these patients, for many of them are sensitive to good food—both before and after thyroid surgery! Very few surgeons study the alimentary flora and fauna of their hyperthyroid patients, the latter especially being neglected. It is a demonstrable fact that the waste products of a few billion alimentary parasites can be most irritating to an already oversensitive thyroid. Remembering that the thyroid gland is a key part of a wide-flung mechanism, we must search routinely for upsets in other parts of the interactive glandular system, notably in the ovaries and the thymus. Defective detoxication clearly exaggerates the responses of the already irritable thyroid, and it is sound therapy when treating the thyroid medically or surgically to see that the associated biochemical inequalities are discovered and controlled simultaneously.

DIFFERENTIAL DIAGNOSIS—The diagnostic phases of this and the other endocrine disorders are adequately outlined in the section devoted to diagnosis (III). It seems, however, that some additional attention should be paid to the matter here, especially to the differential diagnosis, because hyperthyroidism simulates several common disorders, notably heart disease, neurasthenia, and tuberculosis.

Heart Disease—S. A. Levine, of Boston (*Ann. Int. Med.*, July, 1930, iv, p. 67), calls attention to a group of patients usually treated for heart disease in whom the underlying cause is really a latent and unrecognized hyperthyroidism. Even competent internists often overlook it, for the common signs and symptoms usually found in typical exophthalmic goitre and toxic adenoma are not evident in these patients. The diagnosis is even more difficult in patients who have coexisting organic heart disease, such as angina pectoris, hypertensive heart disease, or mitral stenosis. Dramatically interesting are

those with typical anginal attacks in whom proper treatment of the latent hyperthyroidism results in a great reduction in the number of attacks, if not complete relief from symptoms. Levine discusses the diagnostic criteria and directs particular attention to certain points, especially in the general appearance of the patient and in the physical examination, that lead one to suspect the presence of a latent hyperthyroidism. A series of cases is reported, all of which had been treated for heart disease for some time, but in each of which an unrecognized hyperthyroidism was either the sole cause of the trouble or was putting an additional burden on a heart already affected with some other organic lesion. In every one of these cases either complete cure or marked improvement was obtained when treatment was directed at the previously unsuspected thyroid difficulty.

A study of thyroid irritability in its relation to heart disease has been made by T. H. Hanser, of St. Louis (*Jour. Missouri State Med. Assn.*, Jan., 1931, xxviii, p. 6), who seeks to emphasize the fact that thyroid disease may be entirely overlooked as a factor underlying a heart disturbance. Toxemia from the thyroid can cause the most severe forms of congestive failure. However, no matter how severe this failure is, careful medical and surgical treatment directed at the underlying thyroid difficulty offer the patient the best possibility of rehabilitation. In middle-aged persons, unsuspected but later demonstrated thyroid irritability with a B.M.R. of as high as plus 40 can cause mild forms of cardiac disorder in one patient while in another it may produce severe congestive failure. Naturally, the treatment is directed primarily at the underlying hyperthyroidism and not at the heart condition. Hanser's routine consists of bed rest, Lugol's solution for at least ten days, and digitalis only when congestive failure or tachycardia—usually of the auricular fibrillation type—persists despite prolonged rest and treatment.

Neurasthenia—Some neurotic patients present a collection of symptoms that have many points in common with a certain stage of hyperthyroidism. Obviously the different treatment of these two disorders obligates us to differentiate clearly. We must remember that hyperthyroidism may be superimposed upon a neurotic picture though, as we have seen elsewhere (77), hypothyroidism and hypoadrenia are more usually related to neurasthenia.

In his paper on "Practical Points in Hyperthyroidism," David Metheny, of Seattle, Washington (*Northwest Med.*, March, 1931, xxx, p. 140), says:

"The history of a neurotic patient should show that the neurosis has been present not only during the present illness but also before, even back to childhood. Chronic nervous exhaustion is definitely associated with mental stress and strain. If we can show that these factors entered the patient's life at the

onset of the present illness, we commence to doubt actual hyperthyroidism. Mild hyperthyroidism is often preceded by general infections.

"There are other factors that help us to decide. They have been mentioned before by many others. Both hyperthyroid and neurasthenic patients are emotionally unstable, but the hyperthyroid patient has a self-assurance that the neurotic one lacks. The neurotic patient complains much. The relatives of the hyperthyroid patients are the ones that complain. The cold hand is rarely ever found in hyperthyroidism. In hyperthyroidism the nail bed often recedes and causes the patients to complain of sores under their finger nails or that their nails have been hard to keep clean recently. Both groups of patients may be fidgety. The patient with neurasthenia or chronic nervous exhaustion slouches while he fidgets, but the hyperthyroid patient interspaces his purposeful but useless motions with positions of relaxation, to rest tired muscles or groups of muscles. . . . There is one word of warning: One single factor must never make the diagnosis in these doubtful cases."

Persistent tachycardia, when associated with an increased pulse pressure, is, in the absence of an aortic regurgitation, one of the pathognomonic signs of hyperthyroidism. Neurotic patients may have an increased pulse rate but it is not persistent. Again, there is a difference between the muscular weakness of the thyrotoxic patient and that of the neurotic patient. The characteristic blood-pressure is 110/80. H. S. Plummer has a special procedure to differentiate this phase of these two types of cases. He has the patient step up onto a chair; the thyrotoxic patient attempts it boldly and usually fails, whereas the neurotic patient attempts it apprehensively and succeeds.

The cardinal features of thyrotoxicosis are: (1) loss of weight and strength, (2) tachycardia, (3) nervousness and tremor, (4) goitre, (5) exophthalmos, and (6) an elevated basal metabolic rate. The thyrotoxic patient loses weight, but has a very good appetite and rarely complains of indigestion, constipation, belching, flatulence, or abdominal distress. He is tired on rising in the morning.

In his book, "Nervous Indigestion" (New York, Paul B. Hoeber, Inc., 1930, p. 48), Walter C. Alvarez, of the Mayo Foundation, says:

"The physician must be on the watch for signs of hyperthyroidism in every nervous patient and in every one who has lost weight. As he takes hold of the hand he will note that it is warm and moist; the pulse will be rapid and the patient will be weak. Sleep will be poor, and complaint will often be made that the room is close and the air too warm. The diagnosis is easily missed when the thyroid is not visibly enlarged and when the eyes are not prominent."

Tuberculosis—One stage in pulmonary tuberculosis is easily mistaken for hyperthyroidism, and it is quite possible for the tubercle toxemia to irritate the thyroid and confuse one. Such confusion is calamitous, for one must not mistake tuberculosis for hyperthyroidism. The differential diagnosis is based on the physical diagnosis and the sputum examination, as well as on

the reaction to Lugol therapy, for the tachycardia of tuberculosis does not respond to iodine as does the tachycardia of true hyperthyroidism. Basal metabolism is constantly increased in hyperthyroidism but rarely in early tuberculosis, although in more advanced cases the B.M.R. may be changed.

In his paper, "The Differential Diagnosis between Early Tuberculosis and Thyrotoxicosis," Alphonse McMahon, of St. Louis, Missouri (*Internat. Jour. Med. and Surg.*, April, 1931, xliv, p. 170), stresses the various points of difference between these two conditions. He says:

"To my mind the difficulty in the differential diagnosis of early tuberculosis and mild hyperthyroidism lies in the fact that we are dealing in both conditions with the fundamental manifestations of toxemia, affecting the human organism, with consequent disturbance of the sympathetic nervous system, the endocrine glands, the central nervous system, and the cellular physiology of the body. In one, tuberculosis, we have a toxemia caused by the breaking down of the tubercle bacilli and the tissue of the host; in the other, hyperthyroidism, we have manifest in the body an increased amount of thyroxin or an altered thyroxin which has a specific sensitizing effect on all cells of the body with an apparent special predilection for the cells of the vegetative nervous system.

"The result of the toxemia in the early stages of the two states is almost identical. Many general systemic infections in their early toxic phases present such identical symptoms. The similarity of the toxic symptoms in infectious diseases is so striking that we have felt that they are due perhaps to the same mechanism. This necessitates a search for more positive signs of a given disease in the reflex symptoms or the symptoms which in their essence definitely identify the disease.

"The superficial examination of our patients may give us a clue to the diagnosis. The appearance of a hyperthyroid patient is rather typical with the flushed facies and an anxious or eager expression even when exophthalmos is not present. The skin is warm and moist with a general flushing and there is often sweating of the palms.

"The heightened cerebral activity is evident, expressing itself as an eagerness to talk or to answer questions often with a rapidity of speech and a loquaciousness that are somewhat fatiguing to the questioner. The picture is one of a dynamic personality of diminishing potential. . . ."

THE TREATMENT OF HYPERTHYROIDISM is as complex as the disease itself.

First of all, the patient is put to bed with ice-bags over the thyroid and the heart, or both. Detoxication of every description should be instituted because of the hypertoxemia. Alimentary flushing (99), remineralization (100), and special attention to the liver (104) are in order.

Sedatives are a part of the routine of practically every physician; quinine hydrobromide has received considerable praise. The usual dosage is 5 gr.

q.i.d. When the quinine alone does not give results in forty-eight hours, 1 gr. of Bonjean's ergotin is added to each pill.

The spectacular possibilities of iodine therapy have been one of the surprises in endocrinology, for it has long been understood that, in thyroid insufficiency, iodine is a means of encouraging the thyroid to perform its duties. Naturally, then, one would suppose that such treatment would be a detriment in thyroid irritability, but it is not. The reader's attention is called to the consideration of iodine therapy in the Appendix (103).

In view of the fact that hyperthyroidism can be brought about as a reaction of the thyroid to protein substances to which the body is peculiarly sensitive, every effort should be made to find out whether the patient is allergic. If any offending substances are identified, they should be removed from the diet. The same applies to alimentary infections and infestations, because the waste products of these organisms have a detrimental effect not only on the liver and other detoxicating structures, but also on the thyroid. Amebiasis is one of the definite causes of hyperthyroidism, and treatment that is not directed towards an existing infection or infestation is falling far short of its goal.

X-ray Therapy. There are wide differences of opinion regarding the utility of the X-ray in the control of hyperthyroidism. That it is of potential usefulness is beyond peradventure, for many a case has responded splendidly to it. But obviously it cannot reach the various remote causes already referred to, any more than can surgery.

There is, however, a type of hyperthyroidism that is especially suitable for X-ray treatment. Every so often we find a patient in whom careful research fails to disclose any foci of infection or toxemias of the subtle type so often encountered. They are endocrine cases with a previous history of prolonged dysovarism or other endocrine upset. Some of them, having had a goitre for some time, were previously diagnosed and treated as hypothyroid. An interesting peculiarity frequently seen in these cases is a persistent or resurrected thymus, which is quite evident on fluoroscopic examination and sometimes by physical diagnostic means. Just why this organ reasserts itself is not clear, but it is an empirical fact, and sometimes I wonder if there is not some direct antagonism between the thymus and the thyroid after puberty.

P. Hess and H. Schlecht, of Duisburg, Germany (*München. med. Wchnschr.,* Jan. 9, 1931, lxxviii, p. 55), report a series of twenty-nine cases of exophthalmic goitre and hyperthyroidism treated with X-rays in which 93 per cent. were cured or definitely improved. The cases varied in severity, but in nearly all the basal metabolism was raised 20 per cent. or more. The method generally adopted by these workers was to submit the patient to

three series of exposures on successive days, the right and left sides of the neck and the thymus being irradiated each time. (Note that the thymus also was irradiated.) The course of the treatment was controlled by the reduction produced in the basal metabolic rate, and in no case was the patient exposed to further X-rays after it approached normal. Unfortunately, the ultimate response to treatment was often long delayed—sometimes a year or more—and these authors properly point out that this slow response has been disregarded in comparing the results of X-ray treatment with surgical procedures in hyperthyroidism. In other words, we have been too impatient. If these patients can spare sufficient time, these German workers consider that the results of X-ray therapy compare well with those of surgery, while the mortality in the former is *nil*.

Thymus Therapy. While the relation of the thymus to hyperthyroidism is in mind, it might be added that it is passing strange that several of the older reports credit thymus therapy with being beneficial in hyperthyroidism. The history is quite interesting: In 1895, a British physician, D. Owen, decided to treat a certain exophthalmic goitre patient with fresh thyroid, and by mistake the butcher sent thymus. The effects were remarkably good, so Owen tried it again and again. This was the first recorded clinical application of thymus therapy (*Brit. Med. Jour.*, 1895, i, p. 36). Two years later F. P. Kinnicutt, of Boston (*Am. Jour. Med. Sc.*, 1897, cxiv, p. 1), collected sixty-two cases treated with thymus in which thirty-six were improved in varying degree, twenty-five were unimproved, and in one there was aggravation of all symptoms. Twenty years later, S. Solis-Cohen, of Philadelphia (*Am. Jour. Med. Sc.*, 1912, cxliv, p. 13), expressed his preference for thymus extract—from 10 to 30 gr. a day in divided doses—over all other organotherapeutic preparations in the treatment of exophthalmic goitre. This was, of course, only a part of his routine. A dozen other similar reports are found.

ENDOCRINE SYMPATHETIC SEDATION—There is a possibility that organotherapy may be symptomatically helpful in many cases of thyroid irritability. About fifteen years ago, André Crotti, of Columbus, Ohio, devised an original pluriglandular formula, the purpose of which was to lessen the imbalance and sympathetic irritability so commonly found in hyperthyroidism. This preparation contains four ingredients: adrenal cortex, pancreas, pituitary (total), and ovary. For thirteen years, I have used a modification of this formula, in which the original dosage of pancreas is very considerably increased. It is known as Pancreas Co.,* and it has been used by thousands of physicians with symptomatic benefit in many of their cases.

More recently David Marine, of New York, has called particular attention to a presumed functional relationship between the thyroid and the adrenal cortex. He even suggests that the thyroid might be reacting to a defective function of the adrenal cortex. In his article (*Am. Jour. Med. Sc.*, Dec., 1930, clxxx, p. 767), he directs attention to clinical and experimental evidence, which in his opinion support the view

"that a deficiency of some internal secretion of the adrenal cortex and sex glands is one of the fundamental factors in the etiology of Graves' disease, and that the thyroid changes actually represent a compensatory mechanism although often an injurious one."

Marine points out that this syndrome, which rarely occurs before puberty, is from three to six times more common in the female than in the male. By sufficient but sublethal injury to the adrenals, a transient symptom-complex that closely resembles Graves' disease can be produced in the rabbit and cat with intact thyroid. He reminds us that in the newborn there normally occurs a condition somewhat resembling experimental adrenal injuries, namely, the involution of the adrenal cortex.

The only glandular product that Marine has found to be effective in the treatment of hyperthyroidism is an extract of adrenal cortex. In more than fifty cases, the feeding of adrenal cortex caused a striking gain in both body weight and muscle strength. He reports a case of Graves' disease caused by injury to the adrenals following X-ray therapy, and expresses the conviction that in hyperthyroidism a much more fundamental disturbance lies in a deficiency of some function of the adrenal cortex and sex glands, which either provides another means of promoting tissue oxidation or has to do with the regulatory control of these oxidations. The most outstanding manifestation in these cases is clearly a loss of control over these oxidation processes and a resulting physiologic attempt to compensate by an increased production of the thyroid hormone.

The prognosis of hyperthyroidism depends more upon the diagnostic acumen of the physician and the completeness of his discovery and control of the causes than upon any form of drug, endocrine, or surgical intervention. It cannot be overemphasized that no treatment, whether with adrenal cortex or pluriglandular therapy, as suggested, or with Lugol's solution, can directly lessen those underlying factors that are believed to be responsible for the thyroid irritability. Such treatment, then, is a form of temporizing and, if you wish, prepares the patient for surgery; yet, while it is being given, every possible effort should be made to uncover and control the subtle causes.

64. HYPERTRICHOSIS

THE BEARDED lady in the circus commercializes her abnormality. She is an undoubted endocrinopath, whose excessive growth of hair on the face and elsewhere is usually only a part of the peculiar supervention of masculine traits. Although the maximum cases of virilism (97) with hypertrichosis are the rarities seen in the side-shows, the less pronounced types are not infrequent.

There are really two problems of this type—the serious or essentially organic, and the minor or functional. Sometimes a differentiation is made in terminology, and two terms are used in the literature. Whether there is a difference between hirsutism and hypertrichosis, depends upon the definition that is accepted for these terms. In his "Medical Dictionary," W. A. N. Dorland (Philadelphia, W. B. Saunders Co., 15th Edition, 1929) defines "hirsutism" as abnormal hairiness, especially in women, and "hypertrichosis" as an abnormal growth of hair—excessive hairiness. However, Walter Guttmann ("Medizinische Terminologie," Berlin, Urban & Schwarzenburg, 22nd Edition, 1927) considers hirsutism as identical with hypertrichosis, which is an abnormal growth of hair in places where normally there is only lanugo. He gives Apert's definition of hirsutism as "premature development of the whole body associated with disturbances in the sexual sphere, with adiposity, and with excessive and anomalous growth of hair." However, many authors employ these two terms interchangeably.

E. Apert, of Paris, differentiates between hypertrichosis and hirsutism, and draws a distinction between minor conditions of this nature and the modifications in the growth and distribution of the hair in true endocrine disease. For example, we have seen that in hypernephroma (35) serious abnormalities may occur in the sex organs and secondary sex characteristics. The growth of hair, especially on the body, is one of these, and developmental defects of a serious nature may be associated with hypertrichosis.

In his consideration of certain endocrine dystrophies (hermaphroditism, pubertas præcox, hirsutism, obesity) in their relation to adrenal disease, E. Apert (*Bull. méd.*, Dec. 21, 1910, xxiv, p. 1161) says:

"In the subjects we now have under consideration, the hypertrichosis of the body and face does not coincide with excessive development of the hair of the head; it has a special localization; on the face it is the well-developed beard ring, with a slight mustache; on the body, hair—usually thick and coarse—develops on the trunk, particularly in front of the sternum, on the white line, along the dorsal spine, and on the limbs. This special arrangement of hypertrichosis combined with the adiposis imparts a peculiar appearance to these subjects differing from that of ordinary hypertrichosis, which is generally congenital and which affects the hair of the head as much and

more than the cutaneous lanugo. . . . The term 'hirsutism' appears to me to express suitably the condition of these subjects who exhibit special hypertrichosis with obesity, amenorrhea in women, and frequently a heavy voice. . . ."

This disorder is practically always based on anatomical endocrine abnormalities, hence it rarely lends itself to treatment. Quoting from the article by Emil Novak, of Baltimore, in "Endocrinology and Metabolism" (New York, D. Appleton & Co., 1922, Vol. II, p. 627):

"From time to time cases of hypertrichosis have been reported that have been attributed to perversions of ovarian function. A striking case reported by McAuliff is that of a woman of sixty-three, who presented an excessive growth of grayish hair on the upper lip and chin and a moderate amount on the cheeks. The patient had a pelvic tumor, which at operation proved to be a dermoid cyst of the left ovary.

"Hypertrichosis has also been described in association with such anomalies as *uterus duplex* (Hegar), *uterus unicornis* (Freund), and *uterus infantilis* (Hildebrand), and to such acquired conditions as cystic ovaries (Röten) and various tumors (Alberti). It is far more frequently and more characteristically observed in association with disease of the adrenals and occasionally of the pineal. It is perhaps best to consider it as a manifestation of pluriglandular disturbance."

The simple hypertrichosis that sometimes occurs at the involutionary period, or the time when the retrogressive changes in the uterus, breasts, and other essentially feminine characteristics develop, is quite another matter from that due to hypernephroma, etc. Many cases have been reported, often in younger women, who usually were hypofeminine. Treatment directed at the ovarian functions was partially successful. Cases are on record in which hypertrichosis and other symptoms disappeared spontaneously after operation.

Louis Ramond, of Paris (*Presse méd.*, June 22, 1929, xxxvii, p. 821), outlines his routine in what he calls *virilisme pilaire*. He advocates electrolysis for those who have the patience, courage, and money for such treatment; for those who have not, he suggests bleaching the hairs on the face with hydrogen peroxide (applied on cotton for five minutes each day). Ramond is opposed to X-rays; he says that depilatories containing barium sulphide are "irritant without being effective," and is emphatic in his criticism of thallium acetate, "which not infrequently results in a polyneuritis." He advises endocrine treatment of the obvious dyscrinisms "not because any brilliant result is to be expected but because such treatment usually is innocuous and gives encouragement to patients badly in need of it."

However, it is never wise to make any promises in these cases, for the growth of the hair, although theoretically under endocrine control, does not always respond to the regulation of associated endocrine disorders.

65. HYPOCRINISM

FUNCTIONAL INSUFFICIENCIES constitute the majority of endocrine defects and, as has been explained (4), it is quite common to find several of the ductless glands depleted together, causing what is properly called an "endocrine hypofunction."

Some years ago, I suggested the term "hypocrinism" to represent syndromes of this general nature, and it is now an accepted condition of more or less extended endocrine insufficiency or, as it has sometimes been called, "endocrinasthenia." Such a condition does not need to be determined by an extended series of tests; its presence is assumed to exist when the history shows that the patient has gone through a series of experiences calculated to deplete the endocrines.

The diagnosis of hypocrinism in a given case is made, of course, by fitting together several of the usual symptoms that indicate individual glandular shortcomings. For example, a patient who goes through a serious toxemia such as influenza, or who has ptomaine poisoning, undoubtedly will develop a condition of hypocrinism of varying degree, depending upon the extent of the toxemia and the length of time it lasts, as well as upon the endocrine resilience—a most important factor, by the way. Instead of considering only one of the factors—hypoadrenia, for instance—treatment is directed at the several insufficiencies that are associated.

This explains my predilection for pluriglandular therapy and my consistent use, during the last fifteen years, of the tonic formula known as Adreno-Spermin Co.,* which has given a very considerable amount of satisfaction in the common, every-day conditions with which hypocrinism is associated such as the asthenic, depleted state with which one finds reduced tone, poor circulation, low blood-pressure, subnormal temperature, defective elimination, muscular stiffness and achiness, with neurasthenia and a picture that gradually becomes worse and worse, while the real underlying conditions remain misunderstood.

Hypocrinism, then, is a run-down condition in which the endocrines are functionally depleted and for which pluriglandular therapy is both rational and effective.

Elsewhere various forms of endocrine defects are discussed individually. This brief item is inserted to emphasize the necessity of bearing in mind that every patient with hypothyroidism, hypoadrenia, or hypogonadism may be suffering from hypocrinism also and in need of a correspondingly broad endocrine support added to other treatment calculated to encourage and to spare these glands.

66. HYPOHEPATISM

THERE ARE three types of hepatic disorder: (1) The degenerative or structural changes that occur in cirrhosis, acute yellow atrophy, and chronic hepatitis; (2) the biliary disorders in which bile production is retarded—oligocholia and hypocholia; and (3) the detoxicative shortcomings, as a result of which the exchanges in the liver cells are functionally slowed and certain toxemias result. For this last condition I have suggested the term "hypohepatism," to differentiate it from the equally common hepatobiliary insufficiency.

Hypohepatism, then, is a common and important disorder. It may be acute and temporary due to a serious toxic condition such as ptomaine poisoning or the excessive toxemia when, as a result of ileocecal incompetency, the colonic material is backed up into the small intestine. It is caused also by acute alimentary infections or infestations and by chronic difficulties of years' standing. The latter is by far the most usual, and the list of sequelæ is a formidable one.

The diatheses or fundamental perversions of cellular function that manifest themselves in such diseases as gout, rheumatism, and diabetes, *all*, without a single exception, involve the hepatic detoxication; but whether as cause or effect, it is sometimes difficult to decide. At least hypohepatism must be considered as a part of the picture of all diatheses and serious toxemias.

High blood-pressure of the so-called "essential" type is, I believe, one of the manifestations of hypohepatism, and many satisfactory clinical experiences with the liver hormone (45) seem to confirm this idea conclusively.

In the consideration of allergy and protein sensitization (36), I have connected the hepatic detoxicative breakdown with the underlying cause of this peculiar manifestation. I am convinced that it is quite possible to have a form of allergy actually caused by hypohepatism, in which the liver does not completely anabolize the wastes that it should transform into urea, etc. These half-changed protein-split products are neither the original waste materials that reach the liver nor are they the finished nitrogenous end-products. It is suggested that these substances may get into the circulation and become a special offense in some persons or under certain circumstances. Many a patient with migraine will be found to be suffering from just such a condition (72). The obvious therapeutic indication is to hasten hepatic detoxication.

Defective liver function is often found in cases of marked hypothyroidism. The myxedematous patient often has a large, tender, sluggish liver, because the liver cells are infiltrated and swollen just as we expect to find the other

tissues water-logged in hypothyroidism (67). It is sometimes surprising to see what a change takes place in the physical character of such a liver following even one week's treatment with thyroid.

In the toxemias of pregnancy it is logical to suspect stress on the liver with a resultant condition of hypohepatism. The well-known observations of Harold A. Miller and D. Ben Martinez, of Pittsburgh (*Jour. Am. Med. Assn.*, Feb. 23, 1929, xcii, p. 627), on the effect of detoxicative liver extract in the toxemias of pregnancy, support this assumption (84).

One important form of hypohepatism may call for consideration in the treatment of diabetes, because symptoms suffered by some pernicious anemia patients while being treated with liver simulate those frequently occurring with hypoglycemia, namely, marked hunger, headache, nervousness, and sweating. Such observations led Harry Blotner and William P. Murphy, of Boston (*Jour. Am. Med. Assn.*, April 20, 1929, xcii, p. 1332), to study the blood-sugar level in a group of individuals following the injection of a definite amount of liver. Their observations suggest that liver contains a blood-sugar-reducing substance that influences the blood-sugar concentration similarly as does insulin. Quite evidently this blood-sugar-reducing substance may be deficient in hypohepatism. It will be remembered that the French differentiate a type of diabetes designated as "anhepatic."

In obesity, too, a functional hypohepatism frequently occurs, due largely to the pathological changes present in the livers of fat people.

Increasing attention is being paid to the importance of watching the functional capacity of the liver during certain therapeutic procedures that are liable to put additional stress on this organ.

As a result of a comprehensive study of hepatic function by means of several tests (31) in a large number of syphilitics, K. Zieler, of Wurzburg, Germany (*Deutsch. med. Wchnschr.*, March 6, 1931, lvii, p. 393), believes that it is possible to give more intensive treatment, and that this information offers a means of controlling the course of both the liver function during the treatment and the actual treatment itself. Consequently, such investigations enable us to intervene when hypohepatism is demonstrated to be present.

The treatment of hypohepatism is often quite satisfactory, for the liver seems to have an unusual amount of physiologic resilience. It is one of the fundamentals of the treatment of *all* chronic disease, and a measure that can be added with maximum advantage to the indicated therapy of endocrine disease. To avoid repetition, this method has been outlined fully in the Appendix (104).

67. HYPOTHYROIDISM

Minor Thyroid Disorders—Cellular Infiltration—Hypothyroidism as a Symptom—Endocrine Resilience—The Clinical Picture—Diagnosis by Organotherapy—Myxedema—Myxédème Fruste.

THIS SUBJECT already has received some consideration under the title "Goitre" (57), and all the fundamentals referred to there apply with equal force to this extension of my remarks. As a matter of fact, the subjects of simple goitre and hypothyroidism are separated purposely in order to emphasize the numerous phases of hypothyroidism that are not associated with an enlargement of the thyroid gland. As with hyperthyroidism and exophthalmic goitre, so with hypothyroidism and colloid goitre—they may be related, but they do not have to be.

MINOR THYROID DISORDERS—The cultivation in the medical mind of a healthy respect for the thyroid gland would be a great service to clinical medicine. Baffling problems, with non-thyroid symptoms predominating, often yield their mystery to the magic of good thyroid therapy. The thyroid is king among glands and, with strong leadership in the central government, provincial disorders often right themselves automatically.

In spite of the crying aloud from a few housetops, our index of suspicion is still too low. We are dazzled by the cut-and-dried terminal entities, which are quite easily described, almost unavoidably diagnosed, but comparatively seldom encountered.

Two names stand out from the hundreds of writers on thyroid disorders—Eugene Hertoghe, of Antwerp, and Léopold-Lévi, of Paris. It is to these two indefatigable clinicians that the profession is indebted for the present conception of minor hypothyroidism. Hertoghe called it *myxédème fruste* (1891), and Lévi did much to develop the subject to its present magnitude by his book, "La petite insuffisance thyroïdienne et son traitement" (Paris, O. Doin et Fils, 1913), which contains more than 300 pages of concentrated information on a condition which, at that time, was hardly appreciated at all.

The thyroid has been variously called "the keystone of the endocrine arch," "the king-pin among the ductless glands," and "the outstanding and best understood gland of internal secretion"—all of which are perfectly true. No one of the endocrines interferes so effectively in the functions of the other glands, and none is involved more ordinarily in the accepted endocrine pictures than the thyroid gland.

The duties of the thyroid are so numerous and the need for its services so vital that thyroid disorders are very common. No toxemia fails to influence

the thyroid. No nutritional disorder—in either direction—can occur without involving the thyroid. No infection, with the automatic "immunizing response" that nature makes to bacterial invasion, can occur without eventually adding to the burdens of the thyroid. Besides this, the thyroid is responsible for the regulation of the endocrine harmony, and, with the pituitary, has most to do with the initiation and maintenance of the reproductive functions, particularly in the female. No wonder, then, that this gland is concerned in the every-day problems of medicine and must be considered in every involvement of every one of its endocrine fellows.

Parenthetically, it may be added here that the criticism of pluriglandular formulas that "all of them contain more or less thyroid extract, and any good that may be credited to them is probably due to this ingredient," while untrue, has more than a grain of truth in it; for, if one ignores the thyroid aspect of a pituitary disorder, an ovarian upset, or an adrenal problem, the indicated organotherapy may fall woefully short of one's expectations. Perhaps this explains the comment that "the thyroid ingredient in a pluriglandular formula often seems to act as a kind of endocrine condiment that brings out the flavor of the whole."

Hypothyroidism, like hypoadrenia, is of clinical transcendence due to its amenability to treatment and to its implication in so many common disorders where too often it escapes even a suspicion. Several such disorders already have been considered from this point of view. For the sake of clarity and conciseness the references only are cited here: acidosis (34), arthritis (38), childhood endocrinopathies (46), common colds (47), dermatoses (50), deafness (54), headache (59), immunity (68), obesity (79), menopause (80), pregnancy (84), renal disease (86), and rheumatism (87).

The extent and frequency of the lesser changes of hypothyroidism cannot be overstressed. Hypothyroidism is involved in almost all forms of toxemia; it is the point of attack in many endocrinopathies that do not respond to specific glandular therapy, as in dysovarism; it is a feature that plays its vital rôle long before birth, yes, even before conception; and, by its consideration during pregnancy, it is virtually the only hope in the prevention of developmental defects. Then there is the mechanical importance of the principal cellular reaction to thyroid insufficiency—infiltration.

CELLULAR INFILTRATION—The wide-spread extent of the symptomatology of hypothyroidism is due, of course, to the wide-spread influence of the thyroid hormones. By all odds, the most important single thing that happens as a result of hypothyroidism is what has been called cellular infiltration. An understanding of the philosophy of hypothyroid cellular infiltra-

tion uncovers and explains the thyroid features of various syndromes not commonly recognized as endocrine disorders.

The principal hormone service of the thyroid gland has to do with the regulation of the intracellular chemistry. The exchanges in the cell evidently are dependent upon the catalytic influence of the thyroid principles, for when these substances are no longer supplied in proper amount there ensues a cellular inactivity (manifested by the reduced basal metabolic rate) that causes overloading of the tissues with their own half-destroyed waste products. The physics of this coincidence is easily explained: The half-changed products remain in the cell and, in accordance with the fundamental law of osmosis, there has to be an adjustment of the specific gravity of the cellular fluids to equal that of the fluids surrounding the cell. Therefore, additional water is drawn into the cell, causing it to become swollen, boggy, and water-logged. This mechanical phenomenon is responsible for a great many of the symptoms as well as anatomical changes in hypothyroidism of various degrees. It occurs in practically every tissue in the body except those in which it is physically impossible—the bones, for instance.

It is infiltration of the brain cells that undoubtedly is responsible for the dulling of the mental acuity that is so typical of hypothyroidism. Infiltration may give rise to frequent micturition and deafness, to mention two extremes whose explanation will suffice by way of example:

The infiltrated tissues of the bladder wall become swollen, and the upper layers of squamous epithelium are less satisfactorily nourished and more rapidly desquamated. This produces two clinical results: (1) an excess of squamous epithelium in the urine and, as a result of the too rapid denuding of the bladder walls, (2) undue cystic irritability, which causes the frequent micturition.

The lining membrane of the middle-ear, also under the subtle control of the thyroid internal secretions, may become infiltrated and gradually cause, first, noises in the ear (ringing, tinnitus), and later, a functional type of deafness which frequently is not even considered as consequential to any fundamental physiologic cause. Factors such as this are too often overlooked. As a matter of fact, every case of deafness should be most carefully studied from the endocrine standpoint (54) for the very good reason that the nature and function of the tissues making up the important organ of hearing are just as much under the control of the glands of internal secretion as are any other structures of the body.

This brief statement should explain how this same fundamental cellular pathology can cause high blood-pressure—as indeed it does—or menorrhagia,

albuminuria due to glomerular impermeability, alimentary atonicity and ptosis, or, in fact, a score of vitally important conditions.

This same philosophy explains how it is possible for a very limited amount of thyroid, in a suitable case, to bring about so many and so varied changes for the better. Remember, all that is missing in these cases is the capacity to set off the cellular dynamite; when this stimulus is supplied, the chemistry proceeds as it should, the wastes are prepared for elimination, there is no longer a need for the additional material that has caused the infiltration, and the patient is rapidly detoxicated, he loses considerable weight (mostly water), and the symptoms due to the infiltration promptly disappear. This is one of the most heartening of the experiences that we can have with organotherapy; and, too, it is one of the most striking evidences that the endocrines lie vitally at the roots, perhaps indeed *are* the roots, of many of the intricate but very ordinary phenomena that we call physiology or biochemistry.

HYPOTHYROIDISM AS A SYMPTOM—Hypothyroidism, or thyroid insufficiency, is a breakdown in the hormone service of the thyroid gland. It may be functional and limited, or it may involve temporary or permanent changes in the structure of the gland. It may be, and very frequently is, hereditary, or it may be acquired. The degree of hypothyroidism may range from the simplest symptomless shortcomings that pave the way for trouble elsewhere, through *myxédème fruste,* to the ultimate, structural thyroid disease known as myxedema.

One thing about hypothyroidism never varies—it never occurs alone! From the earliest deviation from the functional thyroid norm, long before there is a hint of impending trouble, each related endocrine gland has noted the loss, reacted to it, and has attempted as best it could to get along without the customary thyroid support or to cooperate to offset the effects of the thyroid's shortcomings.

With all due respect to those endocrinologists who stress "The Uniglandular Origin of Certain Pluriglandular Syndromes," as Hans Lisser, of San Francisco, entitles his paper (referred to on page 51), the fact remains unassailable that before a patient notices the evidence which leads to the discovery of an endocrine disorder, long before he is justified in seeking medical advice, the other endocrines have discovered the shortcoming, and the mechanism as a whole has been doing its best to correct the imbalance.

The menopause is a graphic illustration of this, for here an endocrine factor is supposed to pass out of the picture. The hypovarism is *normal.* But all too often the thyroid hasn't sense enough to realize that this is inevitable and proper, and as a result thyroid involvement is peculiarly common, and,

as will be seen in our consideration of the menopause (80), many of the discomforts of this period are due not to the ovarian lack but to the reaction to the well-meant attempts on the part of the associated glands to prevent or replace it.

ENDOCRINE RESILIENCE—So, we must admit that hypothyroidism as a uniglandular condition can occur only in theory. Practically, the endocrine balance is *always* upset, and the extent of the effects of this upset depend entirely upon what I have termed the "endocrine resilience." This factor evidently is what must be credited with the thyroid response to the stimuli that arouse or deplete it. Conditions that deplete the thyroid in one person, stimulate it in another. Some can live in a goitre area and remain unaffected, while others cannot; the reaction varies with the individual.

What is the importance, as well as the basis, of thyroid resilience? It is all-important, representing as it does the difference between health and disease, even life and death. Upon what does it depend? Upon every factor involving the thyroid activities—heredity, toxemia, and stress of every description.

The answer to the question why one person acquires minor thyroid defects as compared with another in the same circumstances, location, or family, is as difficult to give as is the answer to why one person can eat strawberries or shell-fish while to another they are rank poison.

So much for the preliminaries. Now let us consider the clinical aspects of every-day thyroid insufficiency.

THE CLINICAL PICTURE—The patient is indefinably ill with aches and pains here and there. There is a dull headache, which usually is worse in the morning and wears off as the day proceeds. The circulation is retarded. Cold hands and feet, shivering spells, and a real sensation of cold cause the patient to use more clothes or bedding than usual. The skin is dry as well as cold, the hair is brittle, and the nails crack easily. The initiative dwindles away; lassitude and tiredness are the rule. The sleep is disturbed; it is always "hard to get up in the morning"; and the sleepiness during the day interferes with work and pleasure. Yawning is common.

The digestion is upset—the stomach doesn't seem to empty promptly, and there are belching, nausea, and always constipation. Cathartics are effective for a while, but soon wear out. Aspirin helps too, but only temporarily. A home diagnosis of rheumatism is made, for the joints are often stiff and achy and acquire a peculiar tendency to creak (87).

Overweight is quite the rule—a puffy, infiltrated type of flesh with a

decidedly unhealthy feeling that is tender on deep pressure. In women, the gain in weight is often most marked and the menstrual manifestations are changed. The flow is shortened and irregular, the back aches, and during the period of anxious waiting there develop fears and phobias, and nothing ever seems to go right.

The memory is poor, and the forgetfulness spoils the temper—there is a perpetual grouch. Nothing interests any longer: A book is too dry, an odor offends, conversation palls, little things are magnified, and important duties lose their urge. In short, everything is wrong, yet it is all indefinite.

These and perhaps a hundred other vague and variable symptoms weld themselves into a seemingly unbreakable band that can be felt around the head, or around the body, binding the arms to the sides.

There follows the clinical diagnosis: Subnormal temperature, poor urinary elimination, acidosis, hypotension (though this is variable and there is a definite type of hypertension connected with hypothyroidism), a low basal metabolism, and reduced perspiration.

DIAGNOSIS BY ORGANOTHERAPY—Now comes the most spectacular part of the investigation, the diagnostic therapy with thyroid. Two methods are available: a definite, preliminary test of thyroid responsiveness with my Thyroid Function Test (31), or step-ladder thyroid therapy at once. If the latter is decided on, Endothyrin* (24) is prescribed (from thirty to sixty ½-gr. tablets) 1, t.i.d. for three days; then the dose is doubled every three days until effect. The response is amazing; as one has said, "There are not adjectives to describe it." The veil is removed from the mind; and the stiffness, achiness, headache, loginess, and phobias disappear. The outlook is changed as by a miracle—it *is* a miracle! The skin softens, and the infiltration disappears in a few days. Six or eight pounds fall away in as many days, and the bowels are loosened. Everything is changed. This is the *proof* that the diagnosis was right. As Léopold-Lévi aptly says (*loc. cit.*):

"When thyroid therapy controls these diverse symptoms, one must admit that hypothyroidism, in a certain degree, was concerned in their production. Hence the treatment itself acquires a diagnostic value."

Much more might be said—some of it will be found in the consideration of the numerous disorders in which minor hypothyroidism is a factor. Nothing convinces one of the fundamental soundness of the claims of endocrinology more than a few experiences with the organotherapy of hypothyroidism. And, in varying degree, the foregoing picture complicates the majority of chronic diseases, for it is easy to see how the thyroid can become an early victim in all such cases.

MYXEDEMA is another name for the maximum degree of hypothyroidism, and, peculiarly enough, it is essentially a disease of women. Of the recorded cases, 90 per cent. have occurred in women, and it is still more surprising that 95 per cent. of these women were between the ages of forty and fifty.

Of the origin of myxedema little can be said save that it is commonly based on two principal etiologic factors: an endocrinopathic inheritance and previous endocrine stress.

The symptoms of myxedema are as uniform as they are numerous. The skin is buff-pink, sometimes almost grayish in color, also dry and desquamative; the sweat glands are inactive; the hair is dry, brittle, and falls out in quantities; the nails crack easily; the teeth are poor; the vital processes are slowed to a minimum; the temperature is subnormal, and the metabolism is reduced. There are toxemia, constipation, a slow pulse, anemia, and hemoglobinemia. The patient's mentality is dull; he is sometimes termed "logy." The gonad imbalance is manifested in impotence in men, and either amenorrhea or menorrhagia in women.

The condition of the skin in myxedema is pathognomonic—*myx* mucus, *edema* swelling. In fact, many years ago the French neurologist, Charcot, aptly named it *cachexie pachydermique.* Incidentally, two dermatoses somewhat "pachydermic" in character, scleroderma and ichthyosis, are commonly related to major types of thyroid insufficiency (50).

In Chapter 31 various tests are outlined that enable us to differentiate degrees of thyroid apathy or irritability. One of these, the estimation of the basal metabolism, has come to be considered as one of the most important differential diagnostic measures, but its importance as an infallible guide in the study of these cases is being questioned in some quarters. For instance, F. E. Ball, of Chicago (*Am. Jour. Med. Sc.,* Nov., 1930, clxxx, p. 687), suggests that hypometabolism and myxedema are two different things and should not be confused. Myxedema is a definite disease that should be diagnosed clinically and not by a test of the basal metabolism alone. The metabolic rate may be brought within normal limits and yet the patient may still present many of the original symptoms of myxedema. On the other hand, hypometabolism may be diagnosed by the laboratory test and the basal metabolic rate found to be low when the patient has no symptoms. Then, too, Ball finds a group of patients who develop myxedema, or near myxedema, following thyroidectomy, who do not seem to return to normal following thyroid feeding. (The reason is found in the associated glands that cannot respond to the thyroid therapy alone.)

The accepted treatment of myxedema is thyroid extract, which should be given to effect and as long as necessary—*i.e.*, virtually indefinitely. The usual dose is from 1 to 3 gr. a day, though some writers, evidently accustomed to less active products, prescribe 5 gr. three or more times a day. The discovery of the patient's tolerance to thyroid is a coincidence in the treatment. I have outlined a simple preliminary diagnostic method in my Thyroid Function Test (31).

In view of the essentially menopausal character of myxedema, many cases have been treated successfully from the broader endocrine standpoint. It will be found that the ovaries and the pituitary, and sometimes the adrenals, may be encouraged to better activity by simultaneous organotherapy. In other words, the pluriglandular treatment of myxedema at the menopause—with Thyro-Ovarian Co.*—is more satisfactory than thyroid therapy alone. Usually, however, this formula does not contain a sufficient dose of either thyroid or pituitary, and for this reason Gonad-Ovarian Co.* is preferred. To it may be added varying doses of thyroid, according to the patient's changing needs.

The following routine has been used quite a number of times in the successful treatment of myxedema in women, and, although none of them were ever cured, all received more symptomatic benefit than from the thyroid alone that had been used, sometimes for years, before they came under my care: In order to balance the endocrine upset as much as possible, and before giving thyroid to effect, prescribe Thyro-Ovarian Co., 1 tablet q.i.d. for ten days; 2, q.i.d. for ten days (before the expected, but usually delayed flow); then, at the onset of the flow, omit for a week or ten days. This is carried out during the first month or six weeks of treatment, and with it remineralization (100) is always prescribed, for acidosis is one of the most common findings in myxedema. At the end of this time, the formula is changed to the more concentrated Gonad-Ovarian Co., which is given in the same way for six or eight weeks. The patient's weight, appearance, and euphoria are very carefully considered, a record of these having been kept from week to week. Usually the second formula is continued and only then is an attempt made to satisfy completely the thyroid needs of the patient and to determine her tolerance. This is done by giving step-ladder doses of thyroid while continuing the pluriglandular therapy. I frequently order 1 gr. a day for a week, increasing this dose each week by 1 gr. a day and continuing until 4 or 5 gr. or more are being taken daily. Occasionally some patients seem to reach tolerance while they are obviously still in need of more thyroid. In these cases, I give most of the daily dose at bedtime, or, if by any chance it

seems to interfere with sleep, in the morning. In view of the digestive inactivity common in most cases of myxedema, one can profitably give hydrochloric acid at meals, *i.e., with* the thyroid. (See page 395.)

Occasionally what amounts to myxedema follows a needed thyroidectomy, and the problem of treatment is virtually the same, although the previous sympathetic irritability must be taken into consideration. The following question, recently put to me, and the answer, published in the *Hormone* (Sept., 1931, vii, p. 14), apply here:

"Why Thyro-Ovarian Co.* instead of thyroid alone in a case of hypothyroidism following thyroidectomy when there is no menstrual trouble?

"The answer is, of course, that the ovarian function puts such a burden on the thyroid that it is expected that the increasing hypothyroidism will in turn upset the ovarian function; therefore, a part of the pluriglandular treatment here is prophylactic. But there is more to it: The ovaries evidently bring about their demands upon the thyroid by the amount, variations, and character of their internal secretions—these internal secretions get into the blood and remind the thyroid of its duties. This relationship is reciprocal, and it is impossible to tell where the stimulus from one gland to the other gland begins and where that from the other gland to the one ends. The point is, if we deliver to this organization an ovarian hormone, this in itself, when it reaches the thyroid, will make it unnecessary for that thyroid to get so concerned about its ovarian duties. The balance between the thyroid and the ovaries is tremendously subtle and still more tremendously important.

"There is still another vital point to which attention should be called: Here is a girl who has had her thyroid removed and now has hypothyroidism. Is it not reasonable to suppose that the remaining part of her thyroid may be as sensitive to the conditions that brought about the circumstances requiring surgery as was the whole gland before the operation? This being the case, we should not want to give thyroid extract freely. So, instead of replacing the thyroid material with thyroid alone, we are helping to supply the deficiency by giving attention to the associated duties that might and do put stress upon what is left of this gland."

The results from thyroid therapy in myxedema are spectacular, but in only a few cases is the underlying difficulty controlled so that the patient can discontinue the treatment indefinitely. George R. Murray, the real discoverer of thyroid therapy, once told me of a patient who had taken thyroid for thirty years and who, in consequence, had become skilled in fitting the proper dose to her individual needs. The thyroid medication was often discontinued for varying periods, but it was always necessary to revert to it.

Anemia is quite common in ultimate thyroid insufficiencies, and, although the indicated thyroid therapy makes an immediate difference in this phase of the symptom-complex as well as in others, it is a good policy to get through to the seat of the difficulty and try particularly to arouse a better hemopoiesis.

Heparnucleate,* therefore, is an effective supplementary measure and should be given as a part of the beginning treatment of myxedema. It is always necessary to give it for a few weeks, and sometimes an increase of two million has been noted in the red-cell count in this time. Obviously this improves the capacity of these patients to respond to other needed treatment.

MYXEDEME FRUSTE—In 1898, my lamented friend, Eugene Hertoghe, of Antwerp, described a thyroid syndrome that could not properly be called myxedema. It occurs usually in middle age, and the proportion of its incidence in the sexes is not by any means so one-sided as in myxedema. *Myxédème fruste* is a major form of functional hypothyroidism with a series of symptoms quite like those found in myxedema, but less marked.

Since the difference between myxedema and *myxédème fruste* is largely one of degree, the response to treatment varies proportionately. That is to say, the organotherapy of *myxédème fruste* is likely to be curative even though it may take months; and the clinical outcome, therefore, indicates that the thyroid is not irreparably damaged. Naturally, the treatment is virtually the same as that for myxedema and the continuation of the organotherapy depends entirely upon the response of the patient.

Clearly, if *myxédème fruste* is not actually a pathological thyroid difficulty, the treatment should include a very careful search for causes that might be modified, while the organotherapeutic measures are being followed. The successful outcome of the treatment depends very largely upon the discovery and control of thyroid-depleting factors, and, of course, the reestablishment of the endocrine balance.

The treatment of women with this condition is identical with that outlined under myxedema. In men, the principle is the same, only Gonad Co.* is used instead of the ovarian combinations. The step-ladder dosage of thyroid is just as valuable in the male as in the female, and the response to treatment depends entirely upon the physiologic reactivity of the patient's endocrine system as a whole.

Emphasis should be laid on the fact that, in major endocrine disturbances, the associated glands inevitably demonstrate their intimacy by an attempt to carry a share of the burdens of the organ in greatest distress. In so doing, several of the endocrines may have been upset together and, therefore, thyroid therapy of either myxedema or *myxédème fruste* is only a part of the treatment. The regulation of the associated dyscrinisms reestablishes not only the function of these organs but also their beneficial influence on the thyroid itself, thereby lessening the duties of the thyroid and giving it a chance to reestablish itself and accomplish its own duties.

68. IMMUNITY

An Endocrine Opsonic Reaction — Iodine and the Thyroid — Diabetic Infections — Dysovarism — Endocrine Prophylaxis.

ALTHOUGH A reduced immunization response or a susceptibility to infection is not a disease per se, it is discussed here to make clear a very commonly overlooked fundamental, *viz.*, that immunity depends upon the endocrines. Special resistance to disease and unusual susceptibility to it are opposite manifestations of the endocrine resilience.

Why do some people suffer especially from infections? No sooner is one siege over than something else gets them down. Why do some children catch everything that comes along—measles, chicken-pox, whooping-cough, scarlet fever, etc., while others demonstrate an unusual immunity to such infections or infectious diseases? It is largely a matter of the endocrine background.

AN ENDOCRINE OPSONIC REACTION—As a result of the epoch-making researches of von Behring and Ehrlich, Metchnikoff and Pasteur, and many other workers throughout the world, there is a plethora of evidence that the body is supplied with certain autoprotective substances. But the identity of these substances has remained as great a mystery as their source. The numerous agglutinins, bacteriolysins and opsonins, amboceptors and receptors, were all postulated substances, undoubtedly present and active, but still intangible. Years ago Sir Almroth Wright, the originator of vaccine therapy, insisted that the substances produced during the opsonic reaction, *i.e.*, preparing the invading bacteria for destruction by the phagocytes, must be considered as products of internal secretion. Sir Almroth further suggested that several structures other than the then known endocrine glands exercised this incretory faculty.

If we can establish this relationship acceptably, we shall pave the way for the consideration of many a case from the endocrine standpoint; and, having done this, we shall uncover new possibilities in the control of this response.

Sajous, America's pioneer endocrinologist—a staunch friend of mine who, when the criticism of my work was greatest (1919-1922), told me *"Bien faire; laisser braire"*—first lent effective emphasis to the relation between the endocrines and immunity as far back as 1903. In describing what he called a "simplified theory of immunity" ("Internal Secretions and Principles of Medicine," Philadelphia, F. A. Davis Company, Ninth Edition, 1920, Vol. I, p. 298), he showed that the thyroid and the adrenals produce certain substances that are prominent agents in the processes of immunity. When the blood is properly provided with these defensive agents, the

pathogenic agent is converted into eliminable products. The entire process imposes protective properties on the ductless glands involved—thyroid, parathyroids, adrenals, and pituitary. The importance of the thyroid, which Sajous emphasized, is demonstrated by the fact that patients whose thyroid glands have been removed are particularly susceptible to autointoxication.

More than twenty-five years after Sajous' first work on the endocrine aspect of immunity, Y. Tokumitsu reported from the Imperial University, Chosen (*Japan Med. World,* July, 1929, ix, p. 217), a long series of experiments in male rabbits immunized with typhoid bacilli, from which it was concluded that changes in the agglutinating power of the blood can be produced by injections of various endocrine extracts. Tokumitsu believes that there is a correlation between the adrenals, thyroid, and parathyroids in regard to their influence on the agglutinin titer of immune animals. The presence of the parathyroids is necessary for the reduction of agglutination following injections of epinephrine. The reduction resembles that produced by parathyroid extract, and is a result of overactivity of these glands. The increase after the administration of thyroid extract is due partly to hyperfunction of the thyroid itself and partly to hyperfunction of the parathyroids. The correlation of the different hormones and their composite effect on immune bodies differ according to the given functional conditions; and the hormones of the same gland may, at times, have antagonistic effects. As a result of this same series of experiments, Tokumitsu also concludes:

"We have learned the mutual relationship between the endocrine organs using as an indicator the immune bodies and have proved that the uterus, spleen, thymus, and liver, which have always been under discussion as to their hormone function, do evidently secrete hormones."

IODINE AND THE THYROID—There is evidently some connection between the thyroid intervention in the immunizing response and its iodine content. This is especially interesting, for it opens the way to the use of iodine as a prophylactic remedy.

In one of their early studies on the relation of iodine to the thyroid, David Marine and his coworkers (*Arch. Int. Med.,* 1909, iv, p. 440) showed that iodine deficiency causes an epithelial hyperplasia of the thyroid. Microscopic studies of the gland and chemical examination of the iodine content of the tissues showed a marked similarity between these deficiency changes and those that are found in exophthalmic goitre.

More recently, W. H. Cole and his associates in St. Louis (*Jour. Am. Med. Assn.,* April 21, 1928, xc, p. 1274) found that certain infections in various parts of the body bring about a series of changes essentially similar

to those previously shown by Marine to be produced by iodine deficiency. Further work along this line was reported later (*Endocrinology,* Nov.-Dec., 1928, xii, p. 773) showing that the basal metabolic rate is lowered in fulminating infections; in less severe infections, there is an initial drop followed by a rise; and, in milder types, there is a rise but no initial drop. These workers recommend giving iodine or thyroid extract to prevent hyperplasia and to save the colloid in the gland. This tends to keep the basal metabolic rate as well as other conditions normal. Given during infections, thyroid extract or iodine, or both, lessen the initial fall and the subsequent rise in the basal metabolic rate; iodine does this in a greater degree than does thyroid.

The most recent paper by Cole and his coworkers (*Jour. Am. Med. Assn.,* Feb. 9, 1929, xcii, p. 453) confirms their original findings that infections and toxemias produce hyperplasia, loss of colloid, desquamation, and decrease in the iodine content of the thyroid. There does not seem to be any specific organism responsible for the changes that occur in the thyroid, but these workers find that organisms belonging to the group that inhabit the intestinal tract are more liable to damage the thyroid than any others. They have developed a toxin containing four organisms, which, when injected subcutaneously into dogs, causes changes in virtually 100 per cent. of the experiment animals that have not previously been given iodine.

The average iodine content of the thyroid of normal dogs is 0.304 mg. per kilogram of body weight, whereas that of the animals dying from severe infections is only 0.142 mg. per kilogram of body weight. Although similar changes have been observed in human beings, they are not so great. There are many reports in the literature emphasizing the frequency with which foci of infection accompany hypothyroidism; and, too, it has been said, "The development of toxic goitre following infection is too frequent to be a coincidence."

DIABETIC INFECTIONS—The frequency with which diabetics suffer from concomitant infections is well known. The common clinical findings—boils, carbuncles, gangrene—in diabetics indicate that the pancreas has something to do with the response of the body to infections. Small pimples often become serious boils, and these in turn sometimes assume the characteristics of carbuncles and may spread with amazing rapidity. Infections that ordinarily may be considered trivial, frequently become quite serious in the diabetic (52).

In the experimental work on animals it has been found that the removal of the pancreas in one step is almost invariably fatal. The significant fact is that these animals do not die from shock or loss of the digestive services of the pancreas, but from severe sepsis—the wound will not heal. This may

be obviated by the implantation, in the abdominal wall, of a small piece of pancreatic tissue, preferably from the tail of the pancreas, either before or during pancreatectomy. Even a small graft is enough to preserve the immunizing response to infection. This seems to afford the best kind of evidence of a relation between the internal secretion of the pancreas and the power to overcome bacterial invasion.

DYSOVARISM—Special attention is being given here to the relation of the glands comprising the ovarian trinity to immunity. Elsewhere it is shown that dysovarism predisposes to tuberculosis (94) and interferes with the long, hard fight against it. The periodic setbacks suffered by many tuberculous young women who have a hard time each month are not surprising to the specialist. I contend that this same dysfunction is important in its relation to other infections, such as acne, sinus disease, etc. In other words, dysovarism predisposes to infections and interferes with the immunizing forces of the body, as manifested in susceptibility to the common cold (47). It has not been satisfactorily proved whether this is a direct effect or not; probably the thyro-adrenal upset, which so usually accompanies ovarian disorders in women, is responsible.

In my study of goitre and obesity in young girls, it has been especially noticeable that stress on the immunizing mechanism may pave the way to serious endocrine involvement. A point based on this very relationship is emphasized in Chapter 57. It is sufficiently important to be repeated: I claim that acute infectious diseases that occur in girls just before puberty place so much additional stress on the thyroid, which at that time is occupied with the pituitary in the vital duty of initiating and establishing the ovarian functions, that it frequently has to enlarge itself. Even then it sometimes fails in this duty to the extent that we see amenorrhea, oligomenorrhea, etc., which are the prelude to a more or less serious dysovarism. One cannot but admit that this confirms Sajous' claim relating the thyroid to immunity.

ENDOCRINE PROPHYLAXIS—As the reader will see in the consideration of tuberculosis from the endocrine view-point, there is undoubted evidence to establish the fact that the susceptibility to tubercle infections, the response to the associated toxemia, and the capacity of the body to put up an effective fight against this plague are dependent in a large degree upon the glands of internal secretion (94).

If, then, these opinions are reasonable, are we not right in concerning ourselves about prospective difficulties of this nature *before they have materialized?* The prophylactic treatment suggested in the consideration of simple goitre (57) is equally reasonable in the treatment of the other disorders built

on the same foundation. Iodine therapy (103) and thyro-ovarian therapy (80) are actually remedial as well as preventive in conditions of lowered immunity in girls and women. In less degree the same applies to men, especially those who easily succumb to colds, sinus trouble, influenza, etc. In localized infections, thyro-adrenal support is in order. The prophylaxis suggested against colds is as valuable against other infections, and for the same reasons the same procedure is rational as a part of the routine treatment.

A recent communication lends weight to this position. H. J. Lauber (*München. med. Wchnschr.,* March 14, 1930, lxxvii, p. 434) gives the clinical histories of several patients to substantiate his opinion that there is a correlation between internal secretion, predisposition to infection, and healing of wounds. In a man with relapsing furunculosis, examination of the blood revealed hyperglycemia. Small quantities of insulin were injected, and the furunculosis healed in a comparatively short time. Another patient with myxedema had a wound on the hand, which was refractory to the usual treatment, and lymphangitis with high temperature developed. Under the influence of thyroid, the wound healed.

Lauber also reports two other cases in which thyroid preparations favorably influenced the healing of wounds, and one instance in which the combined use of insulin and an ovarian hormone preparation effected healing of an ulceration that for ten weeks had been refractory to other therapeutic measures. On the basis of his observations, the author concludes that, in persons with insufficiency of the incretory organs, endocrine preparations are helpful in the treatment of infectious diseases as well as in the healing of wounds. He assumes that the hormone treatment enhances the defensive power of the organism and increases the actual metabolism in the wounds. In the therapy of wounds, however, the administration of endocrine preparations has to be combined with effective surgical care.

There is much more that ought to be said, but space forbids. Here is a brief item from *Bruxelles-médical* (Sept. 14, 1930, x, p. 1620) that summarizes the subject very nicely:

"While it appears to be impossible to attribute, either experimentally or clinically, to any one particular endocrine gland a large share in the mechanism of immunization, the normal functioning of these glands appears to be one of the conditions essential to the defense of the organism.

"Endocrine disorders constitute the source of special sensibilities, determining media in which anaphylactic phenomena and attacks of asthma or of urticaria will appear. Endocrine deficiencies will cause those affected with them to become more sensitive to infections and will explain the inequality of the resistance offered by patients to disorders of equal virulence."

69. INFLUENZA

Fatigue: Muscular and Circulatory—Adrenal Damage Confirmed at Autopsy—Adrenal Support—Prophylactic Therapy.

ALTHOUGH WE have long been familiar with the epidemic, and sometimes the pandemic, occurrence of influenza, mention of influenza now brings to mind the pandemic of 1918, which spread over the whole civilized world and took an unusual toll of victims. Of those who recovered from the disease, many retained some infirmities, some lasting to the present time.

During that pandemic more than any other, the prostrating and, indeed, pernicious influence of the influenza intoxication attracted particular attention. It is difficult to describe the extreme weakness that the patients feel, and the hopelessness and lassitude that prevent their regaining their health promptly after the acute stage has passed. One point worth mentioning is the great liability to relapse, no doubt owing to the fact that the patients are not able to react to the infection by a full immunity, which must be explained by an unusually severe degree of debility suffered by the endocrine glands, especially the adrenals.

FATIGUE: MUSCULAR AND CIRCULATORY—The symptoms of hypoadrenia are essentially asthenic in character. In fact, fatigue is the principal result, and it may be most severe. The patient is tired out and unable to accomplish his usual mental or physical work. This aggravated degree of muscular asthenia extends to the involuntary muscles causing heart weakness—commonly classed as myocarditis, though there is no real structural change in the heart muscle at the time. The vessel walls lose their tonicity, and low blood-pressure follows with evidences of circulatory insufficiency.

In 1919, a paper was published by D. M. Cowie and P. W. Beaven, of the University of Michigan (*Jour. Am. Med. Assn.*, Aug. 2, 1919, lxxiii, p. 363), giving the clinical evidence involving the adrenals in influenza and influenza-pneumonia.

The possibility of an adrenal cause of the asthenia present in all cases of influenza during its course and during convalescence prompted this investigation. These authors attempted to determine on purely clinical grounds whether hypoadrenia could be shown to be the basis of the asthenia and hypotension so much in the foreground of this disease. Necropsy revealed hypoplasia of the adrenals and evidence of adrenal damage. The occurrence of dysadrenia in influenza may be indicated by the cardinal symptoms and confirmed by the characteristic rise in the reduced blood-pressure which follows a suitably aggressive and prolonged course of adrenal therapy.

Another interesting addition to the literature on influenza is a small monograph, written in 1919 by da Fonseca, of Rio de Janeiro, entitled "Da insufficiencia suprarenal na grippe." In it he cites a number of autopsy findings indicating that changes in the adrenal structures were not infrequent in patients who had died of grippe. These included microscopical and occasional macroscopical phenomena of congestion, especially in the cortex; at times, inflammatory and edematous manifestations were present with leukocytic infiltration, slight hemorrhages, and even foci of necrosis. This Brazilian writer emphasizes the importance of the adrenal aspects of influenza, and insists that the hypoadrenia, which is almost invariably present, is of decided importance as a fatal complicating factor. The adrenal aspects of influenza deserve to be studied and treated in the less serious cases as well as in the severe ones. Many experiences in hospital and private practice convinced him that organotherapy directed at the hypoadrenia is a good treatment. He says:

"Of the reality of influenzal hypoadrenia, modern clinicians are fully convinced, for, in the recent (1918) pandemic which attacked humanity as a whole and to which Rio de Janeiro paid such a heavy tribute, the profession was once again made aware of its importance."

After referring to the paucity of information on the subject in American and European medical reviews, da Fonseca quotes Ricaldoni, of Montevideo, Uruguay, who asserted positively that

"This adrenal insufficiency is inseparable from influenza itself. . . . The adrenal insufficiency of influenza accordingly is more fundamentally significant than that which may appear in all or nearly all the general infections and many forms of intoxications."

It must be remembered that the rôle of the adrenals in acute syndromes had been effectively emphasized by several writers, especially Emile Sergent, of Paris, and the subject has been quite fully discussed under the heading, "Adrenal Dysfunction" (35).

ADRENAL DAMAGE CONFIRMED AT AUTOPSY—Still more convincing proof of the close relation of adrenal damage to influenza emanated from Camp Zachary Taylor in 1919. One hundred and twenty-six patients who had died of influenza were brought to autopsy, and the following findings in regard to pathological changes in the adrenals were reported: In twenty cases no gross changes. In three, frank hemorrhages with the organs enlarged to twice the normal size. In the remaining 103 cases, slight increase in size, definite congestion, cells of cortex slightly swollen. Lipoid exhaustion almost constant. Percentage with obvious adrenal pathology, eighty-five. (B. Lucke, T. Wight, and E. Kime, *Arch. Int. Med.*, Aug., 1919, xxiv, p. 154.)

It has been asked why the adrenals seem to be singled out in influenza. The answer is that they are not; the entire endocrine mechanism is first stimulated and then depleted. If these glands were not stimulated, the body's defenses against such conditions would not be properly aroused, for the thyro-adrenal mechanism plays a vital part in the immunizing response (68).

ADRENAL SUPPORT—It was on this basis, namely, the serious hypoadrenia that proved so characteristic of influenzal and postinfluenzal states, that I based the practical application of adrenal support. At that time, when nothing seemed to be of any signal value in aiding the patient to recover, physicians perforce gave a hearing to my insistence that adrenal support might solve the problem of recuperation from influenza. In those cases in which Adreno-Spermin Co.* (adrenal substance plus spermin plus a tiny dose of thyroid) was prescribed (35), the clinical results were as astounding as they were constant. The effects were both subjective and objective. The blood-pressure was raised thirty or forty points within a week or two. Patients called the medicine "dynamite," and asked why its use had been delayed. They talked about it to their equally depleted friends, who insisted that their doctors find out about this adrenal support and apply it in their cases.

Thus a new idea was established, and hundreds of physicians discovered (1) that they did not have to wait until they had a true endocrine case to utilize organotherapy, (2) that there was something to adrenal therapy and the pluriglandular idea, and (3) that organotherapy was helpful—sometimes amazingly so—even though administered by mouth.

The influenza epidemics of 1918 and 1919 did more to convert the profession to a broader conception of this phase of endocrinology than all the laboratory experiments and theories reiterated through the years.

PROPHYLACTIC THERAPY—It should not be understood that adrenal support is recommended as a remedy for the influenza. Rather, it is directed at the adrenal depletion resulting from the influenza. This fundamental form of every-day organotherapy may be used in a prophylactic way also. It is not a preventive of the influenza itself, but of the postinfluenzal asthenia. It is possible to spare certain glands from the expected outcome of stress and to offer support before they begin to falter.

Exactly this same philosophy has been considered in the chapter on "Common Colds" (47), for there is no difference, except in degree, between the endocrine features of colds and of influenza. The subject is developed still further, especially from the chronic aspect, in the consideration of neurasthenia (77).

70. MAMMARY DYSFUNCTION

Agalactia—Galactorrhea—Mastodynia.

THE QUESTION whether the mammary glands are endocrine organs, does not arise in connection with our consideration of the endocrine therapy of functional disorders of these organs. They are functionally connected with several of the endocrines, and, as we have seen (14), the chief mammary service undoubtedly is subject to the effects of a galactagogue hormone in a physiologic as well as in a therapeutic way.

AGALACTIA—The inability of a mother to produce a sufficient quantity and a proper quality of milk is by no means an endocrine problem. Yet it is apparent that the difficulty frequently can be overcome by recourse to organotherapy, hence it deserves consideration in connection with the endocrines.

It is well known that many animals eat the placenta immediately after delivery. This instinctive habit is not confined to animals, for it is found among certain races in the interior of Brazil, the Sudan, and Asiatic Russia.

Based upon the suspicion that this practice really had a physiologic basis, an attempt was made a number of years ago to feed desiccations of placenta to women who were having difficulty in nursing their infants. Parallel with this, some other workers carried out an extensive series of experiments with small animals. As a result, the galactagogue influence of placental preparations was established. The Hungarian physician, K. Basch (*Monatschr. f. Kinderh.,* 1909, ix, p. 8), whose writings came in for much publicity because of the world-wide interest in the Blazek pygopagous twins, proved that this galactogenesis was due to a hormone influence and had no connection with the nerve supply of the breasts. It will be recalled that one of these twins became pregnant, was successfully confined, and lactation occurred in the non-puerperal sister as well as in the mother. He also showed that the galactagogue effect of the placenta, and even its influence on transplanted portions of mammary tissue, was unquestioned. F. S. Hammett, of Philadelphia (*Jour. Biol. Chem.,* Dec., 1918, xxxvi, p. 569), Bertha Van Hoosen, of Chicago (*Med. Woman's Jour.,* July, 1921, xxviii, p. 169), and E. L. Cornell, also of Chicago (*Surg. Gynec. and Obst.,* Nov., 1918, xxvii, p. 535), have published convincing clinical proof of the value of placenta substance in improving the quality of the milk and the infant's weight curve.

Two other endocrine products—pituitary and mammary substances—have an influence on mammary function, but there have been many contradictory statements about them.

"A new chapter seems to be opened in the hormone control of lactation." This is the closing sentence of an interesting editorial in the *Journal of the American Medical Association* (Jan. 31, 1931, xcvi, p. 359), which was prompted by a consideration of the experimental work of G. W. Corner of Rochester, New York (*Am. Jour. Physiol.,* Oct., 1930, xcv, p. 43), who showed that pituitary extracts exert a positive effect on both mammary growth and function. The effect of the pituitary in physiology as well as in experimental research is proximate, *i.e.,* it is a direct cause of the proliferation and the lactation, but "there may be in pregnancy some other mechanism that restrains secretion" until there is no longer need for this restraint.

In this editorial, the following reference is made to the epoch-making deductions of E. H. Starling, of London—"the father of the hormones":

"A quarter of a century ago Starling and Lane-Claypon, of London, pointed out that, since the mammary gland normally undergoes enlargement and histologic change preparatory to the secretion of milk during pregnancy only, the cause of these modifications presumably lies in some effect exerted on the organism by one or another of the new structures that appear in the pregnant female. Taking into account the marked changes that intervene in the uterus and ovaries, the problem pointed to the possibility that the promoting substance might be derived from the ovaries, notably the corpus luteum, the uterine tissue, the newly developed placenta, or the fetus itself. The British investigators undertook experiments with aqueous extracts of several of these tissues. The extracts of fetuses appeared to give rise to some growth of the mammary glands, but the effect was far less than that seen during a normal pregnancy. These observations were widely published for several years, but they have failed to secure adequate corroboration and have been discredited."

As with several other "discredited" advances in endocrinology, truth will out; and now the clinical deductions of many years once more are confirmed. The galactagogue influence of the hormones from the pituitary and the placenta, as well as from the mammæ themselves, was known long before Starling made his announcements, but products were not available to make these ideas applicable in the clinic.

When, nearly twenty years ago, I suggested the use of extracts of placenta plus mamma and pituitary, the chief basis of criticism was that "there is no evidence that many of these organs have any value whatever when administered by mouth or in any other way." (*Jour. Am. Med. Assn.,* Jan. 18, 1919, lxxii, p. 213.)

Now that the convictions of so many thousands of practising physicians have been confirmed by laboratory workers on animals, it is gratifying to reiterate the clinical claims that have been made these many years.

It happens that clinical experience has demonstrated the interesting and profitable coincidence that, in addition to the galactagogue effect, this remedy exerts a beneficial influence on uterine involution, especially in certain cases of chronic hyperplastic metritis following childbirth. This involutive effect is by far the more important of these two therapeutic services.

GALACTORRHEA—Not infrequently one encounters a woman whose mammary secretion does not dry up properly after the child is weaned. The reason for this probably has nothing to do with the glands of internal secretion, yet, like its antithesis, it sometimes responds to organotherapy.

The procedure that I have recommended with a successful outcome in perhaps a dozen cases is based on general principles: The function of the breasts nearly always is such that it replaces that of the ovaries. Normally lactation does not occur during normal ovarian activity; in fact, the ovaries and the mammary glands are antagonists. Therefore, ovarian therapy directed at the menstrual features of such cases and resulting in the reestablishment of the regular monthly cycle, is physiologically opposed to nursing.

Since, in the majority of these cases of mammary oozing, there was a history of previous menstrual irregularity and ovarian insufficiency, Thyro-Ovarian Co.* was given to all these patients. Coincidentally with the benefit to the menstrual disturbance, there was a control of the galactorrhea in each case.

This same idea may be applied in galactorrhea in virgins or in older women past the menopause—a very rare condition—but there is less probability of benefit. Although the customary local treatment will probably have been administered for some time without success, it is an advantage to continue it with the organotherapy. Local applications of spirits of camphor or belladonna ointment to the nipples, and proper mechanical pressure are indicated.

An interesting and novel clinical incident is reported by L. Kraul, of the University of Vienna (*Zentralbl. f. Gynäk.*, April 7, 1928, lii, p. 873). He asserts that when the distress of milk accumulation in the breasts becomes too great, when suckling is impracticable either because of maternal ill-health or the death of the child, it can be overcome by administering desiccated thyroid twice a day for three or four days. He found that this speedily lessens the secretion of the breasts.

MASTODYNIA—Painful breasts, particularly during the premenstrual period, constitute an early and quite constant symptom of ovarian dysfunction (80). Constant mammary pain, especially if localized and one-sided, is a symptom that may suggest a diagnosis of chronic mastitis or something even more serious. At each menstruation the mammæ are stimulated by the ovarian hormones and, if these hormones are normal in amount and character as

they are in the majority of cases, their stimuli pass virtually unnoticed. But in some women there is an unusual sensitiveness at this time, even considerable pain and tenderness, and sometimes a moderate temporary enlargement.

Recently Max Cutler, of New York (*Jour. Am. Med. Assn.,* April 11, 1931, xcvi, p. 1201), discussed the subject quite thoroughly and expressed the belief that the pathological condition underlying mastodynia, sometimes erroneously called chronic mastitis, really causes a certain type of epithelial desquamation in the ducts and acini, which is accompanied by a local connective tissue hyperplasia. These epithelial cells actually distend the ducts, giving rise to diffuse pain, often accompanied by a generalized nodularity of the breasts. Sir G. L. Cheatle, a British surgeon, who has made a special study of the problem as it relates to the groundwork of cancer, proposes the term "mazoplasia" for this condition.

Sometimes an extreme sensitiveness of the breasts is one of the early manifestations of a menstrual upset, and is of more concern to the patient than the dysmenorrhea, the amenorrhea, or the oligomenorrhea that may be present. It has been noted in a number of cases that the mastodynia is more marked on alternate months; and, as the difficulty has developed, a definite ovarian disease has been found—on the side in which there is more local menstrual pain and with which there is a more general upset.

As we have seen in Chapter 14, the corpora lutea, both of normal menstruation and of pregnancy, bring about decided changes in the mammary tissue. During the stage of proliferation of the corpus luteum, prior to menstruation, epithelial hyperplasia in the mammæ is much more marked. This can be brought about in animals by injections of Endoluteum.*

According to Cutler (*loc. cit.*), in the syndrome in which mastodynia is prominent, the corpus luteum appears so to dominate the ovarian metabolism that there is an excessive stimulation of the epithelial desquamation and increased hyperplasia, which distends the ducts and acini and brings about the pain and tenderness. Based on these conclusions, he has suggested an attempt to correct the pathology. His plan consists in increasing the deficient function of the follicular and interstitial elements in the ovaries, thereby counteracting overactivity of the corpus luteum. This is contrary to the position taken by Hans Lisser, of San Francisco (*Endocrinology,* Jan.-Mar., 1918, ii, p. 12), who reported some interesting clinical experiences following the use of corpus luteum in mastodynia. Cutler believes that such treatment

"... is obviously illogical, since all evidence favors the view that the condition is probably due to excessive corpus luteum stimulation. In fact, the administration of corpus luteum should, and actually has in some cases resulted in an increase of the pain."

At the same time, it has been noted frequently that the overactivity of the corpus luteum suppresses the ovaries and exerts an estrus-inhibiting influence, leading to hypofunction of the follicular and interstitial elements of the ovaries as indicated by the short and scanty menstrual periods in these cases. Ovarian residue is the remedy suggested by Cutler as follows:

Since the most active period of corpus luteum proliferation begins in the intermenstrual phase, patients were instructed to take 5 gr. of ovarian residue t.i.d., beginning fifteen days before the menstrual period and stopping at its onset. An additional 5 gr. daily was prescribed for patients who respond only slightly. This dosage was begun immediately after the cessation of the flow. Fifteen days later this dose was increased to 15 gr. a day. Some patients respond readily as indicated by prompt relief from symptoms and increased menstrual flow. If the periods became excessive, the dose was diminished. It is obvious that no standard dose can be formulated for all patients.

In many patients receiving this treatment there was relief from the pain and tenderness, and also a definite softening of the breasts and actual disappearance of the pain. The menstrual periods in many cases have become more normal. Cutler believes that this effect of ovarian therapy on epithelial and connective tissue changes in the breasts is specific.

Considering the matter from the view-point of the endocrine balance, it will be seen that if these associated hormonic activities are benefited in patients with hypothyroidism or pituitary dysfunction and consequent abnormal ovarian activity, the changed stimuli will regularize the balance between the normal endocrine functions of the ovaries themselves. (There are, of course, at least two functions of the ovaries—stromal and luteal.)

With the foregoing in mind, it is evident that the treatment of mastodynia should be more than local. Applications of belladonna ointment or compresses of spirits of camphor are beneficial. But, since the real difficulty is in the pelvis, to which the mammary pain and tenderness are only reactions, treatment must be directed at the dysovarism also. If this fails to allay the symptoms of the dysovarism and the mastodynia after two or three periods, and particularly if it seems to cause increased pain and local tenderness of one ovary, it may be an indication of the rare condition sometimes called "ovarian poisoning" (80), of which mastodynia may be a symptom.

Some have claimed that mammary therapy is useful as a bust-developer in bosomless women. I have not found it so, but many a time a nursing mother whose mammary development was poor and whose milk was scanty and thin has seen physical development accompany the galactagogue improvement that so commonly follows the indicated organotherapy.

71. MENTAL DISORDERS

Dementia Præcox—Hysteria—Idiocy—Insanity—Psychasthenia.

THE INTRODUCTION to this brief consideration of the relation of the endocrine glands to mental disorder is to be made through the statement of George B. Lake, of Chicago, editor of *Clinical Medicine and Surgery.*

DEMENTIA PRÆCOX—The problem of early insanity is as yet unsolved. The present idea is that the matter is largely a police policy to protect the public rather than a therapeutic procedure to attempt to cure the insane. Let us consider Lake's appeal (*Clin. Med. and Surg.,* April, 1931, xxxviii, p. 235):

"For some years there has been a growing impression among psychiatrists who are seriously interested in endocrinology, that there is some definite relationship, if we could discover it, between certain forms of mental disease, notably dementia præcox, and the glands of internal secretion.

"Sign-posts pointing in that direction are not far to seek. The physical signs of schizophrenia closely resemble those of dysfunctions of various endocrine glands; and definite involvement of these glands is decidedly common in mental patients. The question has been chiefly, which came first—the hen or the egg; the psychic malady or the endocrine disturbance? . . .

"One school of workers feels that the basic endocrine fault is with the gonads, and calls attention to the alleged fact that many, if not most, schizophrenics show stigmata of eunuchoidism. It has even been suggested that testicular transplants would improve the condition.

"In *Clinical Medicine and Surgery* for July, 1928 (xxxv, p. 502), Edward Huntington Williams, of the Psychoendocrine Clinic, Los Angeles, built up a rather impressive structure of presumptive proof of the proposition that an hereditary weakness of the entire endocrine system underlies dementia præcox, probably in all cases.

"R. G. Hoskins and F. H. Sleeper, of Worcester, Massachusetts, reported the results of endocrine studies on eighty schizophrenics (*Endocrinology,* May-June, 1929, xiii, p. 245), during which they administered preparations of the thyroid, gonads, or pituitary to patients whose condition appeared to indicate these substances. In some cases several gland products were administered simultaneously. Their results, while not brilliant, were decidedly encouraging.

"The brains of psychotic patients have been studied fairly extensively and intensively and, except in cases of paresis, the findings have been practically nil, except that the recent practice of encephalography seems to be giving us clues of some kind. Most of the endocrine research appears to have been based largely upon clinical and subjective reports which, while their value is great, if they are prepared in a scientific spirit, do not bring us much nearer to an anatomic explanation in these cases—if, indeed, there be any such.

"For some reason, most of the students in this line seem to have overlooked a report made seven years ago which, to us, seems decidedly significant. This is the article on the adrenals in mental cases, by Sir Frederick W. Mott and Isabel E. Hutton, which appeared in the *British Medical Journal* for July 21, 1923, in which the authors demonstrate clinically that schizophrenics have an unusually and rather uniformly low blood-pressure (especially in the hebephrenic type); and, *objectively,* that the adrenal glands, in one hundred patients who came to autopsy, were decidedly smaller than normal (the decrease in size being almost entirely in the medullary portion, which had practically disappeared in some cases) and were the seat of marked fibrotic changes and of an increase in the number of nuclei, with changes in their size and form.

"There may be, in all these findings, no basis as yet for a rational opotherapy; but we feel that the findings of Mott and Hutton have not been given the degree of consideration that they deserve, and that some men are being held back from the clinical studies which they might make, by the fear that their reports may not be considered 'scientific' by certain of the 'authorities.'

"There is room for a great deal more study, by the laboratory men, of the anatomic changes in the *endocrines* (rather than in the *brains*) of psychotic patients; and there is also room for much carefully controlled *clinical* research, based upon the reasonably solid, if incomplete, foundations which have already been laid."

The Norwegian alienist, Gabriel Langfeldt, of Bergen, has marshaled many findings in a large series of cases of dementia præcox which Williams enlarges upon in his paper, "Psychoendocrine Aspects of Dementia Præcox" (*Clin. Med. and Surg.,* July, 1928, xxxv, p. 502). It will be seen that many of these cases present endocrino-sympathetic anomalies. Thus:

"Stated briefly, one may reasonably expect to find, in a majority of cases of catatonic and hebephrenic dementia præcox: (1) large pupils, with possibly some light reaction anomaly; (2) low blood-pressure; (3) cold, clammy hands and feet, pale or cyanotic; (4) bradycardia or tachycardia; (5) salivation and hyperidrosis; (6) pathologic dermographism; (7) a negative ciliospinal reflex; (8) a positive Aschner's reflex; (9) a positive Abderhalden (Fauser's) test; (10) probably hyperleukocytosis and almost certainly lymphocytosis; (11) a non-sensitiveness to epinephrine; but (12) a hypersensitiveness to pilocarpin; and (13) a positive response to the alimentary glycosuria test . . . even if only 50 per cent. of the above physical abnormalities are found in any given case, we still have a most suggestive group of somatic symptoms that, coupled with the mental symptoms, should be a great aid in diagnosis: also, in treatment. . . ."

Quoting further from Langfeldt's own concluding remarks ("The Endocrine Glands and Autonomic System in Dementia Præcox," Bergen, Norway, J. W. Eides Boktrykkeri A/S, 1926):

"The constitution that is supposed to lie at the foundation of dementia præcox must, of necessity, depend upon a specific inferior endocrine formula. In this essential constitution itself, we have an expression for heredity. The inferiorly constructed endocrine system, besides resulting in the development of the special constitutional type, also results in an inferior development of the brain. When, then, this inferior endocrine system, at puberty or through other accidental causes, is exposed to too great a strain, we get the acute disturbances which we have seen in the acute phases."

The clinical prospect before us is encouraging in proportion to the actual endocrine pathology present. The evidence not only shows endocrine involvement in a generous percentage of mental cases, but that these changes are often structural in nature. So the prospective value of organotherapy is limited by the capacity of the damaged endocrines to respond to it—obviously the time to get best results is early!

At the last meeting of the American Chemical Society (Buffalo, N. Y., September, 1931) R. G. Hoskins and F. H. Sleeper reported their treatment of eighteen cases of dementia præcox at the State Hospital at Worcester, Massachusetts. Thyroid feeding was followed by "significant improvement" in 80 per cent. of this series, five of the cases being sufficiently improved to be released. These writers express the opinion that hypothyroidism is partly responsible for more than 10 per cent. of the cases of dementia præcox in hospitals.

HYSTERIA—The origin of the word "hysteria," from the Greek *hystera,* meaning womb, is an indication that our medical forebears were not far from the correct diagnosis of this condition. Hysteria is essentially a disorder of women and is often built on an endocrine basis, which includes dysovarism and sympathicotonia.

The rule that has been set forth repeatedly in this volume applies very definitely in the treatment of hysteria. If there is a reason for organotherapy, it should be given in conjunction with the inevitably necessary psychotherapy and the usually important general hygienic regulation. It is surprising how subtle and serious the mental and temperamental upset may be when the endocrine balance has been undone.

Many of these cases are essentially ovarian, so the problem simmers down to the treatment of dysovarism (80). Adreno-Ovarian Co.,* my thyroid and ovarian formula plus adrenal substance, for the commonly associated atonic, asthenic manifestations, has been given with benefit to a great many hysterical women who also showed evidences of dysovarism. Of course, it is always a part of other necessary treatment, and it may be admitted frankly

that the results might have been due to the associated measures. However, many a case of hysteria that had been under ordinary treatment for years, has finally received considerable benefit from this organotherapy. When the addition of endocrine remedies to the regular treatment is followed by improvement or cure, it is reasonable to attribute at least a part of the benefit to the glandular therapy. It is not advisable, however, to presume that endocrine upsets are the exclusive basis for hysteria and to depend upon the organotherapy alone.

IDIOCY—Endocrine idiots present an unsolvable problem, because the palpable dyscrinism is accompanied with cerebral damage. The Mongolian idiot, the idiotic cretin, the amaurotic idiot—all discussed under "Childhood Endocrinopathies" (46)—are responsive to endocrine therapy in proportion to the absence of central nervous pathology. Of course, the opposite is true, and the many failures following suitable endocrine treatment are attributable to the structural changes that cannot be corrected. The prognosis in all such cases is unavoidably grave.

INSANITY—Certain types of mental disease, ranging from melancholia to manic-depressive insanity, frequently are built on an endocrine foundation. This is particularly true in women, and it seems that eventually there will have to be a classification of insanity from the standpoint of its causes rather than its results. When this is done, undoubtedly there will be an ovarian insanity and a climacteric insanity.

Suffice it to say that the stress associated with the endocrine unbalance, which includes dysovarism in women, is connected with the causes of mental breakdowns. Although there are many speculations in the literature as to how this comes about, there is no unanimity of opinion on the subject.

A particularly interesting article entitled "Endocrine Therapy in the Psychoses" appeared in the *Journal of Mental Science,* published in London (Jan., 1927, lxxiii, p. 64). The author, C. B. Molony, a medical officer in the Limerick Mental Hospital, reported a five-year experience with the treatment of a series of psychoses from the endocrine standpoint. The majority of these patients were treated with my own Thyro-Ovarian Co.* The summary of Molony's article can be given verbatim:

"Since June, 1922, I have treated fifty-three cases of psychoses by endocrine therapy. Of these, eleven belonged to the adolescent group, and exhibited many features in common with Cases I and II described. There was not a single failure in this group, but I must emphasize the fact that this small series was very, very carefully selected, and includes only those who exhibited undoubted signs of glandular insufficiency. Any case in which

pluriglandular therapy was empirically prescribed has been rigidly excluded here. Five were private patients, all of whom were spared the ordeal of certification—four completely recovered, the fifth is very much improved. There were six hospital cases, and all were discharged . . . 'recovered.'

"The climacteric group is naturally much larger—forty-two cases in all. Of the twenty-seven private cases included in this number, only two required certification during the course of the treatment, and they eventually made perfect recoveries (Case V is one of them). Of the total (forty-two), thirty-four were completely cured, two very much improved, three improved, while there were three total failures to record—possibly because of mistaken diagnosis or long-standing disease, and are the only ones at present in a mental hospital.

"Percentages work out as follows: Treated, fifty-three; recovered, forty-four (83 per cent.); improved, six (11 per cent); not improved, three (6 per cent.).

"These figures are, to say the least, satisfactory, and, taken in conjunction with the critical analysis I have endeavoured to make of the individual cases, afford proof of what I set out to establish, and which I shall, in conclusion, thus summarize:

"(1) No case of mental disorder, more particularly if it supervenes at puberty or the menopause, however advanced or hopeless, should be considered incurable until disordered endocrine function has been definitely excluded, whether this be done by the absence of characteristic symptoms or by the failure of response to organotherapy.

"(2) Endocrine therapy fulfils a very important and useful rôle in the treatment of psychoses in carefully selected cases.

"(3) Compound ovarian extract, in private practice, will obviate the necessity for certification in many cases.

"(4) Polyglandular dyscrasias are the rule in the endocrine psychoses, and pluriglandular therapy should give the highest precentage of satisfactory results.

"(5) The fact that physiologists have not yet succeeded in isolating the hormones or chalones of certain of the ductless glands, and therefore cannot *prove,* by experiments on animals, whether these hormones or chalones are or are not absorbed unaltered from the digestive tract, is no justification for our denying to our patients the benefits clinically proved to accrue from the oral administration of extracts of these endocrine organs."

Since several of the cases reported were typical of classes, three of these reports are given here:

"CASE I.—Female, age 25, admitted December 29, 1924, suffering from a rather severe form of psychosis, manifested by great restlessness, insomnia, profound depression, some degree of confusion of ideas, suicidal tendencies, with hysterical interludes during which she became very excited, and at times violent. Hallucinations of sight and hearing being a prominent feature, a history of recent influenza, the case was at first looked upon as acute confusional insanity or exhaustion psychosis, although the patient, on ad-

mission, exhibited no obvious bodily disease, but was well nourished and in fairly robust health. The usual rest and forced alimentation treatment for exhaustion states was tried for three months without any success whatsoever—in fact, by this time the patient had become almost stuporous. She was put on Thyroid Co. with almost immediate beneficial result, and, as menstruation had been absent for some six months before admission, Thyro-Ovarian Co. was substituted after a fortnight. Result: Menstruation recommenced (before the compound ovarian substance was begun), and patient was discharged completely recovered on May 13, 1925. Pluriglandular therapy was ordered to be continued, patient to report in one month.

"A word about the pluriglandular formula, Thyro-Ovarian Co., which, as mentioned in the notes, I thought wise to substitute for the plain thyroid after two weeks' trial of the latter. Each tablet contains 2½ gr. of ovarian substance with corpus luteum, 1/12 gr. thyroid, and ⅛ gr. total pituitary, and is made up to 5 gr. with a mixture of the phosphates of magnesium and calcium, glycerophosphates, and potassium and sodium bicarbonate. The salts are designed to neutralize the acidosis commonly found in conditions of reduced metabolism, of which hypothyroidism is the classical prototype.

"As I shall have occasion to refer to the use of this formula often hereafter, I may anticipate events by saying that I regard it as a very rational combination, and personally have found it to give uniform results, which justify the price charged. Needless to say the potency of the extracts used is of paramount importance. . . .

"CASE II.—J. M., female age 22, admitted July 6, 1925. First acute attack one and a half years ago. Mental condition more or less abnormal since. Acute exacerbations eight months, six weeks, and two days ago respectively. Severe pelvic peritonitis nine months ago. Appendicitis and complicating oophoritis at laparotomy—appendix and right ovary removed; psychosis subsequently very much aggravated, necessitating certification to private asylum, where followed eight months' treatment on the usual lines with little or no improvement. No history of heredity.

"On admission, restless, hysterical, and spasmodically violent. Fits of crying and laughing. Delusions of persecution elicited. History of progressive insomnia, refusal to remain in bed, constipation, very irregular menstruation, followed more recently by total amenorrhea, capricious taking of food, and repeated attempts at assault on the neighbors. Physical condition poor, but no obvious signs of disease.

"July 13, 1925: Suggestive of manic-depressive psychosis—now in the depressed phase. No symptoms or physical signs referable to the abdomen (including pelvis), if we except amenorrhea.

"January 20, 1926: Six months of routine treatment without appreciable change. Remissions have occurred during which the patient has approached normality, but a mild degree of stupor and dementia, with vacant expression, have persisted. Menses still in abeyance despite hematinics. Mental equilibrium unstable, and the prognosis, as far as complete recovery is concerned, appears hopeless. Blood-pressure persistently low (systolic, 90/95 mm.

Hg.) and general metabolism obviously subnormal. Hence, the next day, put on Adreno-Ovarian Co. Improvement may be described as immediate. Menstruation reestablished in three weeks; intelligence brightened and wits sharpened. Patient now began to live instead of to vegetate. (Habits had been 'wet and dirty' at intervals.) Systolic blood-pressure 110 mm. Hg. Skin (previously rough, dry, and scaly) cleared up and she has not looked back since. Discharged 'recovered' on April 14, 1926; she has since been under the continuous observation of her brother (a medical man with some experience with mental disease), who reported (May 18, 1926) that past failures with various methods of treatment had rendered him totally unprepared for such a complete restoration of her mental faculties. Patient, to his knowledge, had never previously, even before puberty, been, as now, 100 per cent. normal. Advised to recommence glandular therapy on any reappearance of untoward signs. . . .

"CASE V.—The patient was a multipara aged about 41 years. There was a history of insanity in the family, and the onset was closely connected with shock, the sudden death of the husband, aggravated subsequently by financial worries. At an early stage she had a fixed delusion that she was developing cancer of the breast. When I first saw her in her own home she had recently returned from a private asylum, where she had undergone eleven months' treatment. She was practically in a state of chronic dementia—lay like a log in bed, would not speak, eat, or attend to her person, which was consequently in an indescribably filthy condition. I have scarcely ever seen a worse case. As she obstinately resisted all attempts at examination or medical interference, and skilled nursing facilities were not available, I had her certified and conveyed to the Limerick Mental Hospital. Here she spent five months without appreciable improvement beyond the fact that she could be persuaded to take her food without artificial feeding (this had had to be resorted to for the first six weeks). She sat all day long in the day-room without moving or opening her lips, was dull, apathetic, and took no interest whatever in her surroundings; in fact, she was just one of those apparently incurable dements who fill the wards of the mental hospitals. At this stage I decided to try compound ovarian extract. In one month, the patient was able to sew and knit; in two, she played the ward piano in an accomplished manner, and I discharged her nine months from the date of her admission as 'improved'—a conservative estimate of her mentality occasioned by the fact that she still exhibited a certain amount of sluggishness of perception and ideation. She continued to take the extracts, and the final result will be fully appreciated when I state that, on June 9 of this year, I had no hesitation in giving her a certificate of complete recovery and ability to resume her duties as assistant teacher in a national school. Only last week the manager of the school reported that in the performance of those duties she has justified the certificate.

"This is certainly a striking case. Endocrine therapy was tried empirically, if you like, but the result cannot be questioned. Neither can it be regarded as an isolated example of what gland extracts can do in the treatment of the climacteric psychoses."

There is little to add to this clinical report. It has been duplicated by many physicians, and there is a gradually increasing consensus that insanity based on ovarian and related endocrine upsets offers more prospect from a therapeutic standpoint than any other form. Yet, in other cases, the endocrine factor, though present in the most obvious fashion and even responsive in marked degree to the needed regulation, fails to bring about the hoped-for changes in the mental balance. Time and again diametrically opposed clinical experiences occur in cases that to all intents and purposes are identical and are treated alike. Here again the response of the patient's own endocrine glands is the vital factor upon which any clinical improvement must depend, and, unfortunately, this cannot possibly be determined in advance.

PSYCHASTHENIA—The term "constitutional inadequacy" is found in recent literature connected with a syndrome of asthenia that is identical with psychasthenia. These patients probably have an endocrinopathic inheritance, and the underlying cause of their inadequacy is due to their ancestors. Yet much of their trouble is often of their own making—they have little reserve, which they insist on depleting by foolish temperamental, social, or sexual deeds. While we spare the endocrines by means of suitable organotherapeutic support, the good from such treatment depends upon how much of it can be saved up instead of frittered away.

Psychasthenia is a form of neurasthenia in which apprehensions, fears, and phobias are prominent. Sometimes the fears outweigh the real symptoms. Psychasthenia is accompanied with a devastating feeling of mental weakness, utter depression, incompetence, lack of initiative, and inability to concentrate on anything—work or play. Because everything tires the patient, he soon acquires an introspective complex that complicates the problem. Insanity is believed to be just around the corner, and suicide is frequently contemplated. Often this point of view is alternated with a fear of death, and, when some hard-hearted friend comments on the changed attitude, the patient goes into an hysterical attack, or he sulks or weeps copiously. Chief among the numerous subjective symptoms are headache, vertigo, paresthesias, and shooting pains in various locations. Insomnia is the rule, and dreams add to the instability. These patients are always complaining that they wake up more tired than when they went to bed.

A *faux pas* in etiquette, the necessity for smelling an unpleasant odor, a draught at a meeting or party, dirt on the cutlery or crockery, dysharmony in a musical number, a dream that cannot be recalled completely—these are only a few of the insignificant factors that are supposedly the cause of psychasthenia. Soon these things become obsessions and no reasoning seems to avail.

Psychasthenia is a disorder of the intelligent, and usually there is much concern over the etiology. The diagnosis is barren of real clinical disease. These patients "know that there is nothing the matter" with them, yet they wander from one specialist to another exaggerating their feelings and manufacturing troubles.

The psychasthenic patient usually is toxic, anemic, sympathicotonic or vagotonic, and practically always has what I have termed "endocrinasthenia." Frequently there are clear-cut signs of endocrine upset, which, when more or less casually explained, give the patient a new slant on himself and a new hope. At least it is something to attack, and it should be used as a means of doing something more for these poor souls. Psychotherapy will help some, but psychoanalysis should be taboo—these patients have done too much analyzing already. Many a case is "cured" by Christian Science; in fact, this is apparently the outstanding type of disorder likely to respond to that method.

From the view-point of endocrinology, however, there are some really encouraging prospects. Several functional dyscrinisms can actually cause a clinical picture comparable with psychasthenia—the thyro-adrenal syndrome such as follows influenza, so-called neurocirculatory asthenia, or the shell-shock of war times. If a neuropsychosis is definitely connected with symptoms of thyroid, adrenal, or gonad dysfunction, the early response to such indicated therapy frequently makes a great difference in the outlook. As hypoadrenia is an outstanding feature of these cases (35), adrenal support is of real prospective merit. Adreno-Spermin Co.* is an effective weapon in the fight that these patients must make. An increase of twenty or thirty points in the systolic pressure and the euphoria that usually accompanies it, give the patient a feeling that something is really being done. This improvement should be judiciously played up—it is more logical for the physician to emphasize this improvement as an earnest of still greater betterment, than it has been for the patient to respond unfavorably to the emphasis of his discomforts. It should be remembered that the first results from needed hormone regulation can be turned into psychic weapons. For this reason hypodermic endocrine therapy with Adreno-Spermin Co. or with Adreno-Cortin* (9) is particularly helpful, for, besides its symptomatic effects, this treatment keeps the patient in closer touch with the physician and enables the skilled doctor to impress his psychotherapeutic powers so much the more.

Suffice it to say that the fundamental principles that have been established as a result of the consideration of neurasthenia as an endocrine problem apply in the consideration and treatment of psychasthenia, for psychasthenia is neurasthenia (77).

72. MIGRAINE

Migraine as an Anaphylaxis—Hepatic Features—Ovarian Migraine—Pituitary Therapy in Migraine.

THE CHARACTERISTICALLY periodic hemicrania called migraine is evidently a deep-seated constitutional disorder, often hereditary. Women suffer from this peculiar intense headache three times more frequently than do men. Migraine is often associated with other manifestations of dyscrinism. Consequently the endocrine aspects of migraine are taking the place of the purely neural and toxic bases previously considered necessary to the etiology. There are many predisposing factors in migraine, such as physical or mental fatigue, depressed states, thyroid dysfunction, genital disorders, toxic conditions, and disturbance of the special senses.

MIGRAINE AS AN ANAPHYLAXIS—In 1923 J. L. Miller and B. O. Raulston, of Chicago (*Jour. Am. Med. Assn.*, June 30, 1923, lxxx, p. 1894), suggested that there are points of close similarity between migraine and hay-fever, asthma, and urticaria. Patients with migraine show a periodic variation in their susceptibility and immunity. Certain foods have been known to bring on an attack of migraine much as they produce allergic responses. These Chicago workers have stressed the value of non-specific protein therapy, which is undoubtedly spectacularly helpful in some cases (105).

More recently R. M. Balyeat and F. L. Brittain, of Oklahoma City (*Am. Jour. Med. Sc.*, Aug., 1930, clxxx, p. 212), connect migraine with allergy. Their conclusions are based on the study of fifty-five patients ranging from 6 to 68 years of age in whom a family history of allergy was elicited in no less than 95 per cent. In one-third of these cases the onset occurred in childhood. The exciting factor is probably always a specific sensitivity to one or more foreign proteins, and treatment should take this into consideration. It is stated that the results of treating migraine as an allergic disorder are as good or better than those obtained in nearly any other chronic disease.

My own conclusion is that the offending substances may be intermediary protein waste products, which for various reasons are not properly anabolized by the liver (66). However, at least one other predisposing factor is necessary, for many a case of most serious hepatic detoxicative breakdown shows as the principal result a functional hypertension (45) rather than migraine.

HEPATIC FEATURES—The migraine picture—with toxemia, fierce headache, biliousness, and other abdominal features—always has reminded me of an hepatic disorder. I have never failed to stress hepatic therapy in migraine; it does not always cure the patient, but it helps a great deal.

As our knowledge of the endocrine character of the liver has been perfected (since 1925), it has been possible to accomplish still more in migraine by means of the hepatic detoxicating hormone (13). In this connection, the reader is asked to consider the brief discussion on hypohepatism (66), for I am convinced that migraine is caused largely by this disorder.

There are others who connect the etiology of migraine with liver dysfunction. For instance, D. D. Comstock, of Los Angeles (*California and West. Med.*, March, 1928, xxviii, p. 380), concludes:

"2. That it is primarily and essentially endocrine in character. . . . 3. That either directly or indirectly it involves a specific liver dysfunction. . . . 5. That the sympathetic nervous system is involved probably through a correlation with the endocrine system. . . ."

Joseph S. Diamond, of New York (*Am. Jour. Med. Sc.*, Nov., 1927, clxxiv, p. 695), reports thirty-five cases of cephalic and abdominal migraine in which liver function tests were carried out. The results indicate a definite liver disturbance. He discusses the inability of the liver to detoxicate putrefactive substances derived from animal proteins in the intestinal canal, and considers the resulting symptoms as an allergic reaction. He adds:

"The understanding of migraine becomes much simplified when we consider that toxic putrefactive substances reach the general circulation through the failure of the liver to synthesize and detoxicate them. A series of symptoms then arise which are the result of vascular changes in the cerebrum or other viscera, which may be regarded anaphylactic in character and are analogous to Quincke's edema."

Other variations of the idea of the hepatic character of the basis of migraine are found in a paper by C. W. McClure and M. E. Huntsinger, of Boston (*New England Jour. Med.*, Dec. 27, 1928, cxcix, p. 1312), in which they state that disturbances in lipoid metabolism, abnormal state of the liver function, and positive protein sensitization reactions are definite pathologic findings that have been demonstrated in migraine. This suggests that hepatic dysfunction plays an important part in the production of migrainous symptoms.

According to Albert H. Rowe, of Oakland (*California and West. Med.*, Nov., 1930, xxxiii, p. 785), the nausea and vomiting that are associated with migraine may be of central origin, or they may be due to a localized concomitant allergic reaction in the liver or gastro-intestinal tract.

D. F. Fraser-Harris, of London (*Brit. Med. Jour.*, Dec. 13, 1930, ii, p. 1025), emphasizes the fact that the liver is constantly destroying poisons more or less perfectly in different individuals. In some, it detoxicates so perfectly that the poison never accumulates and consequently these persons never have headaches; in others, the liver traps the poisons less perfectly so

that some are always escaping into the circulation. When the toxin accumulates beyond a certain concentration in the blood, the syndrome of hemicrania is established. The exact period of this toxic situation may be seven, fourteen, thirty, or forty-two days, thus producing the weekly, fortnightly, monthly, or six-weekly headache. In other words, the rhythm of the migraine is suggested as being dependent upon a preexisting rhythm in hepatic detoxication.

OVARIAN MIGRAINE—Some writers insist that there is an important ovarian feature in the majority of cases of migraine, and its greater incidence in women would seem to confirm this opinion.

There are two explanations: (1) That dysovarism interferes with a part of the normal cellular detoxication, thus leaving duties to be performed elsewhere. For instance, a thyroid defect, such as is extremely common in dysovarism, could put an additional burden on the liver which might be the last thing to cause the toxic storm so often found in migrainous patients. (2) That changes in the ovaries themselves cause to be discharged into the blood a perverted internal secretion, which is the actual exciting cause of the attacks. This is comparable with the condition known as "ovarian poisoning" (80). The menopause often puts an end to migraine. There are in the literature a number of records of the disappearance of migraine following ovariectomy; and "the induction of an artificial menopause by the use of radium has cured some patients."

PITUITARY THERAPY IN MIGRAINE—Renewed interest in the empirical use of pituitrin in migraine has been aroused by the report of E. F. Hartung, of New York (*Med. Jour. and Rec.,* Nov. 19, 1930, cxxxii, p. 497), whose clinical results seem to substantiate the theory that migraine is a manifestation of pituitary dysfunction. The results in his series, which includes a large number of cases over a period of several years, seem to prove the untenability of various theories that have been propounded regarding the etiology of migraine.

The results in a group of fifty patients who were treated with special reference to anaphylaxis were entirely negative. Although constipation and carbohydrate intolerance undoubtedly influence specific attacks of migraine and must, therefore, be taken into consideration in treatment, they are not believed to be a basic cause of the headaches.

In the course of his study of migraine, Hartung has found several factors pointing to an endocrine basis: The onset of migraine regularly occurs at puberty; it commonly ceases in women at the climacteric and in men at the age of declining endocrine activity; it is absent during pregnancy; specific

attacks are often induced at or near the menstrual period and during sexual excitement; and the attacks occur regularly. The endocrine theory is corroborated also by the fact that an excessive carbohydrate intake induces attacks of headache, because the pituitary aids the pancreas in controlling carbohydrate metabolism. Hartung adds:

"We believe that migraine is a manifestation of a pituitary hypofunction, that for ordinary life the pituitary is adequate, but under stress and strain, physiological or emotional, the pituitary is called upon for increased activity, suddenly enlarges, and produces the picture we call migraine."

Treatment was formulated, based on this idea. It was demonstrated clinically that an attack of headache may occasionally be aborted by the hypodermic administration of posterior pituitary extract. Improvement has followed the oral administration of pituitary substance also. Of fifty patients who were carefully studied and treated in this manner, twelve were almost entirely freed from attacks; thirty-five were greatly benefited, the attacks being less frequent and less severe; and in only three was there complete failure. The treatment was as follows: Hypodermic injections of anterior and posterior lobe pituitary extract, or of whole gland extract, were given twice a week for a month, then once a week thereafter as long as necessary. Oral pituitary therapy was given in conjunction with the injections.

Twenty-five years ago Deyl suggested that acute enlargement of one or both lobes of the pituitary might account for most of the phenomena witnessed during an attack of migraine. This idea was elaborated by Walter Timme, of New York (*Jour. Nerv. and Ment. Dis.*, Dec., 1919, l, p. 460), and several others.

Several years ago a similar idea was advanced in Europe. A Norwegian, K. Zeiner-Henriksen (*Tidsskr. f. d. norske Lægerfor.*, March 14, and April 1, 1928), tells of having treated forty-two cases of migraine with pituitrin during a period of two years and nine months, and of having achieved what he calls "prolonged improvement" in twenty cases. An intramuscular injection of 0.5 cc. was given once a week. In discussing the rationale of this treatment, this author suggests that it may break a vicious circle, the existence of which depends on faulty functioning of the pituitary body, which at times does not produce an adequate secretion on account of some psychic disturbance or other cause. He holds that pituitrin is more effective than other symptomatic remedies, even luminal.

The plan outlined in the Appendix (99, 100, and 104) spares the liver and the endocrines as a whole. While it is being carried out, the thyroid, ovarian, or allergic features may be developed and treated accordingly.

73. MUMPS

EPIDEMIC PAROTITIS is an acute, self-limited infectious disease of bacterial origin. The salivary glands are the tissues usually involved, practically always the parotids, but metastatic involvement of the endocrine glands is by no means infrequent.

[It may be worth mentioning here that a number of experimental researches have been carried out to establish the suspicion that the parotids actually produce a hormone. Parotid extract has been used in an empirical way, and, surprisingly enough, it once had quite a vogue in the treatment of ovarian dysfunction.]

The sequelæ make mumps a disorder of decided endocrine interest, for the incidence of orchitis, or more rarely ovaritis, with permanent endocrine and exocrine damage to the sex glands, is quite high. According to the figures given in Cecil's "Text-Book of Medicine" (Philadelphia, W. B. Saunders Co., 1930), orchitis follows in from 15 to 30 per cent. of the cases of mumps in young men and boys and atrophy results in about 53 per cent. of those so affected.

Many references are made in the literature to damage involving the pancreas, thyroid, adrenals, and mammæ, besides the gonads. But the great danger from mumps is gonad atrophy. Now that the sex hormones are tangible, potent entities, those who have discovered their therapeutic value naturally are hoping that they contain prophylactic potentialities, by means of which a part of the endocrine damage can be mitigated.

Lydin,* the standardized male hormone, has been used as a prospective preventive of Leydig-cell damage with results that are quite indeterminate so far. At least two points are worth emphasis: (1) Lydin is of proved value in functional hypogonadism; but (2) it has no value in ultimate testicular atrophy and total aspermia. Theoretically such a measure should enable us to lessen the gonad phase of mumps, but who can know in advance what the extent of this damage will be? As a matter of fact, the degree of the gonad involvement following an attack of mumps has no relation to the severity of the course of the infection. Apparently simple cases may result in serious testicular damage.

A daily injection of the standardized Lydin solution during the active period of the attack is suggested as a prophylactic measure. This seems especially rational in certain cases when it is recalled that the incidence of orchitis is believed to be increased by previous testicular trauma or inflammation.

74. MUSCULAR DISORDERS

Asthenia—Myasthenia Gravis—Neuromuscular Dystrophies—Paralytic Myasthenia.

THE TYPICALLY muscular character of the outstanding symptoms of adrenal insufficiency has stimulated many a neurologist to investigate the possibility of an adrenal phase to certain of the more marked and organic muscular dystrophies. First, however, let us consider "the commonest symptom in the whole range of medicine"—asthenia.

ASTHENIA—The fatigue syndrome is, of course, a muscular disorder, yet it is so common that asthenia is almost always considered as a symptom incidental to other troubles. Pathological tiredness, or myasthenia, is a symptom of several definite endocrine disorders. It is the outstanding feature of Addison's disease and other less serious degrees of hypoadrenia. It is the rule in hypothyroidism, and the more marked the insufficiency the sooner the patient tires. In hyperthyroidism, too, the fatigue syndrome is as usual and as marked as in its physiological antithesis. In fact, the endocrine functions are so closely related that it is rare to find dyscrinism without asthenia.

As endocrinasthenia is a part of a larger syndrome, its treatment must vary with the cause. It may be said, however, that the fatigue syndrome should never be treated as such—with stimulants, tonics, etc., for in most instances the trouble is due to overstimulation and more prodding surely is unwise. A distinction must be made between the tonic effect of endocrine therapy and the stimulating influence of strychnine, coffee, or quinine. Endocrine therapy is a real support to the depleted glands—it replaces their normal product (substitutive organotherapy); it arouses their function by catalysis (homostimulative organotherapy); and, when pluriglandular therapy is given, it spares the overworked associate organs from a part of their duties.

There are three direct measures whereby asthenia can be combated: (1) endocrine support usually to several glands together, for a general cause cannot limit its effect to only one gland; (2) the neutralization of the acid wastes in the tissues and the blood by remineralization (100); and (3) hastening the action of the chief detoxicating mechanism, the liver, thereby sparing the system (especially the endocrines) from the undestroyed wastes that a defective hepatic detoxication permits to pass the liver barrier (104).

MYASTHENIA GRAVIS—Developments in the study of neurasthenia, with its extreme myasthenic picture, and especially the accomplishments in the treatment of this symptom-complex by means of adrenal support (77) have sharpened the interest in the possible connection between the adrenal

glands and true muscular dystrophies. Although I cannot believe that damage to the central nervous system such as one finds in several paralytic conditions is susceptible of modification by treatment directed at the ductless glands, it is true that not every symptom is of purely central nervous origin. Some cases have functional features that may be modified by controlling the concomitant endocrine irregularities.

Some years ago, F. H. McCrudden, of Boston (*Arch. Int. Med.*, Feb., 1918, xxi, p. 256), collected sufficient clinical and laboratory data to establish a relationship between adrenal dysfunction and progressive muscular dystrophy. Without going fully into the details of his extensive studies, he reports that the severe myasthenic condition pathognomonic of this disease is fundamentally due to hypoglycemia which, in turn, is the result of a defective glycogenesis, the ingested carbohydrates being changed into other elements than the glycogen necessary for the normal muscular nutrition. The cause has been attributed to deranged adrenal functioning, and this offers some hope to those suffering from what has heretofore been considered as a hopeless disease.

The adrenal phases of myasthenia gravis are fully discussed in a comprehensive article by Arthur P. Noyes, of the Rhode Island State Hospital (*Rhode Island Med. Jour.*, April, 1930, xiii, p. 52). He says:

"The best results have been secured by the use of suprarenal extract. . . . In myasthenia, suprarenal extract gives results that can be obtained by no other endocrine therapy. . . . Recent experimentation seems to show that in myasthenia the extract acts much more by a biological process whereby the products of muscular activity are rendered inert than by a simple stimulation of vasomotor nerves. . . . These results cannot be secured by adrenalin."

Besides the adrenal possibilities in myasthenia gravis, which are purely symptomatic in prospect, there are some clinical findings connected with this disease that direct attention to other endocrines. For instance, autopsy has uncovered a persistent thymus more times than can be considered coincidental. Changes in the thyroid are not infrequent. It has been recorded by several writers that there may be a noticeable improvement in the myasthenia during pregnancy. These findings arouse suspicion of some endocrine defect, and occasionally organotherapy confirms it. These patients receive subjective benefit from adrenal cortex, but it is not curative.

In 1918 I saw three cases labeled myasthenia gravis, and in two I was able to follow the effects of adrenal therapy for two years or more. To all three cases it gave undoubted symptomatic benefit, which would fade away on discontinuing the treatment and improve again on resuming it. Now that a standardized and much more potent product is available in Adreno-Cortin,*

which is known to be active through its influence upon the muscular chemistry, there should be new prospects in the treatment of this condition. But again it must be emphasized that the endocrines cannot regenerate nerve tissue.

NEUROMUSCULAR DYSTROPHIES—There is some opinion in favor of an endocrine consideration of several muscular dystrophies, based undoubtedly on clinical conclusions following the administration of organotherapeutic products. Far be it from me to deny these possibilities, but there is a great difference between the endocrine treatment of a patient with Thomsen's disease (myotonia congenita), Little's disease (spastic paraplegia), Huntington's chorea, or some other neuromuscular dystrophy, and the endocrine treatment of the disease itself.

Most of the patients with these conditions are sent in as endocrine puzzles; usually they are defective children. Undoubtedly it is possible, even probable, for a child to have a central nervous disease and an endocrine disorder, clear-cut or indefinite. Organotherapy is then advisable. Frequently there is improvement which, because of the previous grave prognosis, is magnified by the parents and often by the physician. The real damage remains; the myodystrophy is left virtually unchanged. I have seen scores of patients in whom organotherapy produced real benefit to the associated dyscrinism but never to the organic nerve damage. Endocrine treatment of muscular dystrophies, which is that of the developmentally defective child (46), is never advised for less than six months, and it is only fair to make early and frank explanations to the parents about the limitations of the measures.

PARALYTIC MYASTHENIA—According to Henri Claude, of Paris, the Erb-Goldflam syndrome of paralytic myasthenia is a muscular asthenia based on endocrine insufficiency. Claude says that the endocrine glands are normal, or even increased in size, but that they are functionally exhausted by a truly excessive effort. This is believed to be due to the entrance into the circulation of poisons of varying origin, which directly affect the nerves and muscle cells.

This French writer believes that, in the Erb-Goldflam syndrome, the multiple endocrine insufficiency (hypocrinism) is a secondary reaction, just as the disappearance of spongiocytes in the adrenal cortex is a change secondary to an intense or prolonged muscular agitation.

Where paralytic myasthenia is associated with definite central nervous lesions, the control of the latter cannot be brought about by adrenal cortex therapy. On the other hand, Adreno-Cortin* induces symptomatic, musculotonic benefit in these cases so long as it is continued, exactly as has been found to be the case in certain patients with the parkinsonian syndrome (81).

75. NARCOTIC ADDICTION

THE ADDICT is an endocrinopath, and his trouble has been caused by endocrine overstimulation. Before we can appreciate the glandular phases of drug addiction, however, we must consider the relation of the beginnings of the habit to the ductless glands.

To be stimulated by poisons and toxins in order to bring about circulatory and detoxicative reactions that eliminate these irritating substances from the organism is one of the adrenal functions. There is an adrenal response to every case of poisoning just as there is to every case of focal infection.

Continued irritation by varying stimuli—toxic or emotional—wears out the adrenal glands; they become depleted, and hypoadrenia ensues. The action of strychnine on the adrenals illustrates the point. G. N. Stewart and J. M. Rogoff, of Cleveland (*Jour. Pharmacol. and Exper. Therap.*, May, 1919, xiii, p. 95), in studying the action of strychnine on the production of adrenin by the adrenals, found that the drug causes marked but temporary increases in the output of this principle. Doses of strychnine that are well within the therapeutic range and that cause little or no exaggerated reflex irritability, considerably augment the rate of the output of adrenin. In fact, the phenomenon is best seen with smaller doses of the drug given subcutaneously.

It is reasonable, then, to suggest that already overstimulated and depleted adrenals need support rather than even an ordinary dose of strychnine, and organotherapy may be a valuable adjuvant in the recuperation process.

Alcohol, arsenic, mercury, quinine, morphine, and any of the opium derivatives act in essentially the same manner as strychnine. They stimulate the adrenals to hypersecretion, which inevitably is followed by hypoadrenia. This should be borne in mind by those who are forced to use these drugs in a clinical way.

The fact that coffee is also a stimulant is evidenced by the common complaint of headache and loss of pep when regular drinkers miss their morning cup. Undoubtedly manufacturers of coffee substitutes exaggerate the evil of coffee, but there is no denying the fact that caffeine is in the same class of endocrine-stimulating substances as strychnine and other similar drugs. There are times when stimulants are essential, but I wish to emphasize the folly of giving adrenal stimulants to patients whose adrenal glands are already worn out by prolonged stimulation.

The importance of the adrenals in disposing of morphine has been verified by some interesting experiments conducted by A. Torino and J. T. Lewis, of Buenos Aires (*Am. Jour. Physiol.*, July, 1927, lxxxi, p. 405). They

made a series of studies of the influence of morphine on adrenalectomized rats and found that healthy rats, well fed and protected from cold, survived double adrenalectomy in quite a number of cases. (If they die, they usually do so within five days of the operation.) A series of adrenalectomized rats, having evidently recovered from the operation, were given small doses of morphine (0.04 mg. per gram of body weight) two weeks after the adrenalectomy. This dose, which was only one-tenth the lethal amount for normal rats, caused 70 per cent. of them to die. The conclusion is that the adrenals have something to do with the capacity of the body to overcome the effects of morphine and similar substances. This is confirmed in the story of the cat and the flea powder (page 83).

The influence of virtually all drugs on the glands of internal secretion is that expected from their influence on the organism as a whole. The stimulants stimulate and later deplete, the sedatives sedate and later deplete, and the alteratives alter and later deplete. Useful stimulation, as with strychnine and allied alkaloids, soon becomes a detriment, especially if the patient has been suffering from a combination of stimulating circumstances and the organism already has been overstimulated until it has given out. On the other hand, the cellular sleep caused by narcotics puts the endocrines to sleep also, and consequently their activity is slowed. The accumulated intracellular toxins then add their weight to that of the drugs themselves.

It matters not whether the narcotism is attributable to the most vicious of the ensnaring drug principles, as morphine or cocaine, or to some milder forms—the endocrines suffer. The more subtle the ensnarement, the more sure the endocrine involvement. Soon, to the ordinary wastes of the organism and the excessively poisonous drugs, are added the endocrine wastes—the glandular ashes and clinkers—which clog up the endocrine mechanism and burden it still further.

The picture of the narcotic addict without his customary morphine or cocaine is one of utter depletion. And why are not the endocrine glands depleted with the rest of the body? There can be no doubt whatever that this is true. It is not only a logical conclusion, but is proved in two decisive ways: (1) The patient manifests a train of symptoms that include hypoadrenia, marked muscular asthenia, and reduced arterial tension; hypothyroidism, including lowered metabolism, subnormal temperature, and abnormal sensations of chilliness and cold; hypogonadism; and, in verity, a dire hypocrinism. (2) Many times the attempt to influence these depleted glands by suitable organotherapy is notably helpful—a fact that most effectively confirms the previous impressions.

The drug addict is constipated, toxic, and dehydrated. Each of these conditions facilitates the initiation, the maintenance, and the aggravation of the endocrine phases. The emotional aspects also play their part in complicating matters. Fear, rage, pain, worry, and privation, all exaggerate the serious detrimental effects on the endocrines, for, as has been so aptly shown by Walter B. Cannon at Harvard and confirmed times without number, the emotions out of control first overstimulate then deplete the thyro-adrenal mechanism, if not the entire endocrine chain.

The endocrine picture of the withdrawal period, that nightmare of cellular insanity through which the patient must go to reach the dawn, is clear-cut and undoubted; but it is not yet the rule to supplement the accepted routine by organotherapeutic means. However, it is done by some, and it is as rational as any other form of endocrine therapy.

Referring to the endocrine phase of the withdrawal period, M. G. Carter and Edward Huntington Williams, of the Los Angeles County General Hospital (*Med. Jour. and Record,* June 18, 1930, cxxxi, pp. 597, 598), state: ". . . it is our belief that there is a close association between the withdrawal symptoms of opiate addiction and the endocrine system, especially the adrenals. . . . We incline strongly toward the belief that the letting down of the adrenal system is responsible for many of the withdrawal symptoms."

Again, in his book, "Opiate Addiction" (New York, The Macmillan Co., 1922, p. 156), Williams says:

"It is probable that the muscular weakness is due to a depletion of the endocrine glands, a case of hypocrinism. If the opiate addiction has been of long standing this condition of endocrine inactivity has become chronic and correspondingly difficult to stimulate into normal activity.

"If this theory is correct the indication for treatment is to stimulate and encourage the depleted glands of internal secretion as quickly as possible, and to attempt to replace this absence of normal secretions by the administration of artificial endocrine preparations."

The picture of narcotic addiction, then, must be conceded to include a generalized pluriglandular depletion of general origin. Since the adrenals and the thyroid seem to be involved to a greater extent than the other glands, they should always be considered first. Thyro-adrenal support—with Adreno-Spermin Co.*—has proved its soundness in the ultimate endocrine upset of drug addiction as it has in the almost as bad endocrine depletion following influenza. But during the withdrawal period there is no limit to the dose—give 1 or 2 sanitablets every hour or two, and an intramuscular injection of 1 or 2 cc. of the corresponding solution an hour for three, four, or six hours a day during the greatest stress; then reduce the dosage sharply to 1 or 2 tablets q.i.d., and 1 or 2 injections a day.

76. NASAL DISORDERS

OTORHINOLOGISTS ARE now utilizing organotherapy to hasten the healing and epithelization of chronic ulceration of the nose and adjacent sinuses. The principle underlying this comparatively new method is based on the clinical application of the ideas of H. W. C. Vines and W. R. Grove, of Cambridge University, which gave to the profession a new conception of the means whereby ulceration is controlled (95).

The philosophy of this treatment hinges on the calcium content of the blood and its regulation by the parathyroid hormone. This is not the place to discuss the physiological action of the parathyroids (16) or the chemical changes that come about in parathyroid disease (81); but it may be said that the effect of the parathyroid hormone or the formula, Para-Spleen Co.,* on septal ulcer or sinus ulceration is no different from its effect in chronic middle-ear disease (54).

As will be seen in the consideration of otitis media, stress must be placed upon *the need for drainage*. Parathyroid therapy practically always brings about a local reaction in all ulcerative areas, increasing the amount and modifying the character of the exudate. There must be an exit for this sero-purulent material.

Whether the increase in the utilizable calcium in the serum, or other chemical changes in the tissues at the base of the ulcer itself, bring about the healing is not known; but it does not matter much. The point is that parathyroid therapy is indicated in all forms of ulceration from sprue to tuberculosis.

The rhinologist must remember that the pituitary gland is very close to certain structures that interest him particularly. Dyspituitarism may cause actual symptoms in the posterior pharyngeal space. The reader is directed especially to the chapter on headache (59) and to the following statement of a specialist, J. A. Glassburg, of New York (*New York Med. Jour.*, March 15, 1922, cxv, p. 362), who expresses himself regarding pituitary headache in rhinological practice thus:

"I wish to emphasize the facts that there is a definite, distinct type of headache which is met quite often in rhinological practice; that this headache is due to a disturbance of the secretion of the pituitary gland; that it may exist concurrently with nasal pathology; that it is wholly independent of this pathology; that it is not relieved by nasal operations, but responds to specific endocrine medication and, finally, that in order to diagnose this type of headache yet render proper treatment . . . it is absolutely necessary to obtain a complete anamnesis, do a thorough physical examination, and employ the laboratory aids requisite."

77. NEURASTHENIA

Endocrine Overstimulation — A Thyro-Adrenal Syndrome — Adrenal Pathology in Insanity — Adrenal Support — Thyroid Therapy — Ovarian Neurasthenia.

TOM WILLIAMS, of Miami, Florida, one of the most convincing American writers on neurasthenia, defines it thus (*Am. Med.*, Aug., 1917, xxiii, p. 582):

"Neurasthenia is a structure of the imagination, highly embellished with additions that have been made from time to time by many individuals, until it has become a huge edifice of which the characteristic features are weakness, lack of endurance of mind and muscle, and all the possible results of that weakness in its effects on internal organs. . . . Hypoadrenia may result from the wasting of old age, the toxins of the infectious diseases, . . . or perhaps from exhaustion by long-standing emotions. Neurasthenia, we may realize *is* hypoadrenia."

The nervous breakdown is a very real clinical entity, even though many neurologists now believe that the term "neurasthenia" is but "a cloak to cover shortcomings in diagnosis." There is no doubt that the condition commonly understood as neurasthenia is a decidedly variable complex, the factors of which differ widely in their origin and manifestations. Naturally, the diagnosis "neurasthenia" is an incomplete one, and satisfactory treatment is attainable only when fundamental causes are understood and controlled.

In my monograph, "Neurasthenia as an Endocrine Syndrome" (April, 1921, Pp. 92), a large amount of evidence is gathered from the literature to show that the run-down neurasthenic patient practically always has dyscrinism even though it may not stand out above all the other symptoms.

ENDOCRINE OVERSTIMULATION—As we have already seen, all forms of stimuli to the endocrine glands first increase their functioning and then play them out, provided their physiological elasticity is not unlimited. Overstimulation *must cause depletion*. It happens that the adrenal glands are extremely important in maintaining the tone of the sympathetic nervous system as well as that of both striped and unstriped muscles. The subtle chemical reactions of the body, such as detoxication, depend upon the hormonic encouragement of the adrenals. In addition to this, the sympathetic system stimulates the adrenal glands; therefore, both cause and effect are related. Consequently, toxemia such as one finds accompanying chronic foci of infection or acute infectious disease, or resulting from a breakdown in the hepatic detoxication, causes an undue functional activity of the adrenal system; and, the greater or more serious the stimulus, the more likely the resultant hypoadrenia.

In his address, "The Clinical Importance of the Sympathetic Nervous System" (*Brit. Med. Jour.*, June 14, 1913, i, p. 1257), S. A. Kinnier Wilson, a prominent London neurologist, makes the following pertinent remarks:

"Many of the common symptoms of neurasthenia and hysteria are patently of sympathetic origin. . . . There does not appear to be any tenable distinction between the asthenia of Addison's disease and the asthenia of neurasthenia. Cases of the former are not infrequently diagnosed as ordinary neurasthenia at first. It is difficult to avoid the conclusion that defect of glandular function is responsible for much of the clinical picture of neurasthenia. . . . Sympathetic tone is dependent upon adrenal support, and, until the glandular equilibrium is once more attained, sympathetic symptoms are liable to occur."

It is true also that emotional stimuli exert their principal influence on the adrenals and, through them, on the thyroid and other endocrine organs. A very common cause of adrenal irritation, and later of adrenal insufficiency, is emotional overstimulation. Hence it can readily be seen that the adrenal glands are liable to be functionally involved in a large number of cases; and, dependent upon their resilience and capacity to come back, the body is very liable to be deprived of a part of their service.

When the ordinary symptoms of hypoadrenia are enumerated, it will be apparent that there is some intimate relationship between this condition and neurasthenia, for the symptoms of both manifestations are practically identical. So uniformly is this the case that Leonard Williams, of London (*Practitioner*, July, 1917, xcix, p. 1), once said:

"The real neurasthenia or shock is a circulatory matter. . . . The proper circulation of the blood is second only in importance to its proper composition. Its composition is determined by the efficiency partly of the excretory organs, and partly of the ductless glands. . . . As to treatment—how is one to treat this except by the sedative of a purified and well-composed blood supply? The purification refers to drainage, and the good composition to the tribute of the endocrine glands. Of the former I will say nothing; it is so banal that few ever consider it! With regard to the latter, I permit myself to fling wide my restraint in a parting shot, and boldly call attention to the practical identity of the symptomatology of the real neurasthenia with that of *adrenal insufficiency*."

A THYRO-ADRENAL SYNDROME—Let us recall the picture of the patient with thyro-adrenal insufficiency. The first and transcendentally important symptom is that he is all tired out and has neither initiative, reserve, nor that attribute so commonly called "pep." The circulatory efficiency is remarkably reduced; the temperature is subnormal, and the patient suffers from cold, especially in the hands and feet. He has other evidence of circu-

latory stasis, and, still more important, the blood-pressure usually is much below the average normal. The elimination of wastes is carried out just as half-heartedly as every other function of the body is performed. A reduction of from 50 to 75 per cent. in the urea output is not unusual.

These persons are peculiarly atonic; and, since the atonicity involves the alimentary musculature equally with that of the cardiovascular mechanism, intestinal stasis is the rule. Consequently, autointoxication is aggravated and a vicious circle is formed. This atonic picture often may assume most distressing forms: apathy, disinterestedness, and even some types of insanity that are built upon this same essentially endocrine foundation.

Scores of expressions agreeing with this position may now be found in current medical literature, but there is space here for only one. The subjoined statement is taken from an editorial in the *Journal of the American Medical Association* (Dec. 18, 1915, lxv, p. 2166):

"The typical neurasthenic generally has a disturbance of the adrenals on the side of insufficiency, the blood-pressure is almost always low and the circulation poor. It is believed that many individuals presenting the classical symptoms of neurasthenia with low blood-pressure, decreased mental elasticity, mental and physical depression with the fear that they cannot now accomplish their usual good mental work, with the story that they have 'lost their nerve,' with a vacillating and indecisive frame of mind, are suffering from functional hypoadrenia."

ADRENAL PATHOLOGY IN INSANITY—It may be mentioned in passing that adrenal dysfunction, as well as actual adrenal pathology, is often found in insane persons. Some years ago, the famous British alienist, Sir Frederick Mott (*Brit. Med. Jour.*, July 21, 1923, ii, p. 95), reported that in 143 cases of dementia præcox the average blood-pressure was comparatively low, and in one hundred cases brought to autopsy "the adrenals were smaller than in any other class of cases studied to date" (71).

Twenty years ago, in reiterating things that had been learned while on a trip to France, I made the statement that neurasthenia of all conditions deserves to be studied and treated as a condition in which dysadrenia is the most important fundamental factor. Until the endocrine aspect of neurasthenia was brought to the attention of the profession, its treatment was essentially a negative one. By this is meant that a change of surroundings, increased elimination, and enforced rest—both physical and mental—were the customary measures employed. This is negative treatment merely because it removes the fundamental factors, leaving the body to recuperate as best it can. Of course, such therapy is perfectly rational, because fatigue (and neurasthenia is endocrinasthenia, or adrenal fatigue) cannot be over-

come without rest. However, it seems much better to give a treatment that is more positive and direct in its action, *i.e.*, while the causes are being controlled advantageously and the overworked organs are being rested as much as possible, *encourage the depleted endocrine mechanism that is so fundamentally at the bottom of this syndrome.* The many clinical applications of this idea have proved it to be "a revolution in the consideration as well as in the treatment of neurasthenia."

All functions dependent upon sympathetic maintenance, or in the regulation of which the autonomic nervous system plays a part, become deranged as a result of this serious chemical irregularity, and bad inevitably becomes worse with inexorable rapidity. The neurasthenic syndrome always appears hopeless to the sufferer, and too often to his physician also. It is no more difficult to give functional support to the adrenals than to render a corresponding service in hypothyroidism.

ADRENAL SUPPORT—The fundamental therapeutic principle of adrenal support applies in neurasthenia just as it does in any of the other manifestations of hypoadrenia. The administration of an organotherapy calculated to encourage the exhausted adrenal system is just as rational as to offer other forms of homostimulative organotherapy in the hope of increasing the functions of the ovaries, thyroid, or any of the other glands.

The tired-out, run-down patient invariably manifests evidence of a compound endocrine disorder. The ductless glands as a system are just as depleted as the remainder of the organism as a whole. General causes, such as influenza or some persistent toxemia, inevitably produce general results. It is impossible for such conditions to affect the adrenals alone. But, to be Irish once more, suppose this were really possible, would not the original uniglandular hypoadrenia deplete the associated glands both by the added toxemia and by the lack of the normal endocrine stimuli from these glands?

Now that the adrenal cortex hormone has been isolated and Adreno-Cortin* has been found of service in such widely varying conditions as Addison's disease, the cachexia of malignant disease, or the muscular tire of paralysis agitans, the tendency has been to look for well-advanced organic cases before advising the indicated therapy. This is as wrong as limiting the use of thyroid therapy to myxedema. The farther away from an ultimate organic dyscrinism one finds the patient, the more likely is he to respond to the much needed endocrine support.

Since the endocrine aspects of the majority of cases of neurasthenia are of paramount importance—first, as we have seen, in the study of these difficult cases; and secondly, as is being emphasized here, in their successful

treatment—considerable emphasis has been given to the value of thyro-adrenal support by the results of more than fifteen years' experience with this method of treatment.

THYROID THERAPY—Since it is of capital importance, particularly when confronted with hypocrinism (65)—generalized endocrine insufficiency—that these endocrine organs should deliver to the body the vital chemical messengers that initiate and maintain so many important functions, a corresponding pluriglandular support is in order. The thyroid is often involved also. From my monograph on "Neurasthenia," already mentioned, I quote the following as pertinent here (page 80):

"If the neurasthenia is based on a lessened thyroid activity and a consequent accumulation of unoxidized wastes, which irritate and deplete the nervous chemistry and reactivity, this hypothyroidism must first be discovered and then treated as any other hypothyroidism. Attention has already been called to the advantage of my Thyroid Function Test as a means of determining the presence of an early thyroid apathy, and, if this test indicates that such a condition is present, thyroid therapy is the only rational method of treatment. It is impossible to replace the missing thyroid hormone, no matter how small or how large the deficiency may be, in any manner that can compare, both in logic and results, with organotherapy. The minor thyroid aspects of neurasthenia, to my way of thinking, are next in importance to those of dysadrenia. Thyroid therapy many times can be added to adrenal therapy, so the pluriglandular insufficiency involving both of these glands may be treated simultaneously with better results than if only one of these two aspects were discovered and attacked.

"So, to all the fundamental measures, add a well-balanced thyroid therapy, and by this I mean enough of the thyroid extract to encourage the thyroid without driving it. On the other hand, if the thyroid gland has already been overstimulated and is functioning to excess, and there is a psychoneurotic element due to a latent or obvious hyperthyroidism, then the treatment should be directed at the endocrine cause as well as at the other causes of this cause."

The removal of as many interfering factors of an emotional character as possible and the maintenance of a restful environment should be observed in conjunction with the pluriglandular therapy, which is as follows:

In both sexes the formula, Adreno-Spermin Co.*—the combination of total adrenal substance, spermin from the interstitial cells of Leydig, and a small dose of thyroid, used in hypoadrenia (35)—may be prescribed: one sanitablet at meals and at bedtime. This original pluriglandular treatment of neurasthenia is given with the expectation of encouraging the endocrine glands so uniformly depleted in just such cases. This dose is usually large enough, though in certain cases it may be advantageous for a while to give 2 tablets three times a day, or even 2, four times a day. This formula should

be given for at least two months, even though the results may seem to be entirely satisfactory before the end of that time. In grave cases, and particularly when it is advisable to watch the patient carefully, this formula may be supplemented with the corresponding solution. An intramuscular injection is given daily for a week or ten days, then every other day for the rest of a month. It is not advisable to use injections without the oral formula.

OVARIAN NEURASTHENIA—In neurasthenic women in whom the ovarian factor is marked, the problem almost always involves dysovarism. Quoting again from my monograph (pages 81, 83):

"In ovarian dysfunction accompanied with neurasthenia, the necessity for regulating the dysovarism obviously is of paramount importance. In many of these patients we find such a combination of circumstances that it is difficult to determine which of the causes is first in importance. Whether the neurasthenia is a result of this dysovarism or is an independent, entirely dissociated condition, the thing to do is to treat them both at once. Never mind whether the organotherapy has the credit for the ultimate benefit or whether it is due to the other regulatory measures that you have advised. Literally thousands of women who have acquired a neurasthenic habit in conjunction with amenorrhea or some other form of dysovarism have found their neurasthenic tendencies disappearing as soon as suitable treatment, including indicated pluriglandular organotherapy, had modified the disturbed hormone function of the ovaries and the related glands.

". . . An excellent thing about the organotherapy of neurasthenic states is the diagnostic advantages that sometimes come with this treatment. As Léopold-Lévi has so aptly stated, if one finds that 'thyroid treatment suppresses various symptoms, one must admit that a thyroid insufficiency has been present, that in a certain measure the results of this have been acting upon those functions controlled by the thyroid gland, and that thyroid therapy is, therefore, of diagnostic value.' And, naturally, this applies to other similar measures."

This phase of the subject is considered more fully in another chapter (80). The suggested treatment is Adreno-Ovarian Co.,* but, if as often happens there is no notable dysovarism, Adreno-Spermin Co. is preferable.

Certain cases of so-called "neurasthenia" are complicated by sympathicotonia (91), a condition quite the opposite of asthenia. The usual apathy, inactivity, and cellular torpor are replaced with irritability, nervousness, and hypersensitiveness. When the unusually low tension of hypoadrenia is absent, as is often the case, this type of endocrine stimulation is not required. The estimation of the basal metabolic rate or the Thyroid Function Test (31) usually will show that these patients have latent hyperthyroidism. In this event, best results follow the use of the sympathetic sedative formula, Pancreas Co.,* coupled with the therapeutic routine suggested elsewhere (63).

78. NEURITIS

Neuritis and Hypothyroidism—A Clinical Test with Thyroid Therapy—Neuritis at the Climacteric—"Neuritis" Often a Muscle Pain—Multiple Neuritis.

THE TERM "neuritis" refers here to painful nerves, and is used in the same improper sense as we use the names "neurasthenia" and "rheumatism." It does not refer to acute infections of the nerve sheaths nor to anatomical damage to the neurons. Neuralgia is, perhaps, the preferable name.

NEURITIS AND HYPOTHYROIDISM—One of Léopold-Lévi's emphatic statements about the minor thyroid insufficiencies has to do with neuritis. From his pioneer book, "La petite insuffisance thyroïdienne et son traitement" (Paris, O. Doin et Fils, 1913, p. 12), I translate just one sentence:

"The same applies to . . . a whole series of neurotoxic disorders that represent in general the incidents of neuro-arthritism, which thyroid treatment is capable of ameliorating or entirely suppressing."

Neuritis, like rheumatism, is a toxemia. When it is associated with hypothyroidism there not only is an accumulation of waste products, which irritate the sensory nerves, but the nerve-cells themselves as well as the nerve sheaths may be infiltrated just as other tissues are infiltrated (for an explanation of this process, see page 473). Infiltration naturally causes pressure, and the pressure causes pain, or neuritis.

The fleeting pains and the neuralgia of thyroid origin are really neuritic. Perhaps many readers may not know that fifty or more years ago myxedema was supposed to be a nervous disease for this very reason. Further on in Léopold-Lévi's book (*ibid.*, p. 213) is a paragraph bearing upon this:

"Prior to the knowledge of the physiologic functions of the thyroid body, myxedema was regarded as a nervous disorder. There is now no doubt that it is an affection which, at the very least, is predominantly of a thyroid nature and that most of the disturbances, particularly those of the nervous system, to which it gives rise are the result of insufficient thyroid function. Likewise, a good number of functional disorders of the nervous system must be classed with the *fruste* forms of myxedema."

A CLINICAL TEST WITH THYROID THERAPY—Not all cases of neuritis are of this nature, however. The estimation of the basal metabolic rate has not always proved a differential measure in my hands, for I have seen several cases of neuritis that responded to thyroid therapy when the metabolic rate was somewhat higher than normal. Usually many of the signs of hypothyroidism are present. The best proof of the reality of the

underlying thyroid factor is the response to the organotherapy, which at times gives more prompt and lasting relief than aspirin or other analgesics.

NEURITIS AT THE CLIMACTERIC—A form of neuritis of this same essential character is not uncommonly found at the climacteric, and here the reason for the endocrine upset is more satisfactorily explained. The treatment, of course, is that of the menopause (80).

When confronted with a case of nagging neuritis, it is not bad practice to try some of the fundamental supplementary therapeutic measures such as alimentary flushing (99), remineralization (100), and, of course, hepatobiliary encouragement (104). Then, after the decks are cleared, give thyroid in gradually increasing doses to effect, starting with half a grain a day. If the supplementary measures have relieved the neuritis, the thyroid need not be given. It is none the less true that such treatment may be in order, for the list of measures just recommended is as rational a means of sparing a thyroid or thyro-adrenal mechanism as any other.

"NEURITIS" OFTEN A MUSCLE PAIN—The current connotation of the word "neuritis" is admittedly wrong, for what is often called neuritis is not even a neuralgia but rather a muscle pain, a myalgia, due to the accumulation of toxic substances in the muscles. This common syndrome may be built upon a detoxicative defect due to hypothyroidism, already mentioned, and to hepatic insufficiencies both biliary and detoxicative. With these there invariably is an advanced degree of acidosis.

The general treatment is directed at the liver (104), with remineralization (100); and, if the suggestion about myalgia is correct, the adrenal cortex hormone may be used to encourage more directly the muscular chemistry (74).

MULTIPLE NEURITIS—The syndrome with this label does not always seem to be the inflammatory condition that the name indicates. The definition of T. Grainger Stewart, of Edinburgh (*Brit. Med. Jour.*, Sept. 12, 1925, ii, p. 461), is as follows:

"I propose to include under the term 'multiple neuritis' all cases in which, as the result of a general cause—toxic, infectious, or metabolic—the symptoms present point to a more or less simultaneous affection of many of the peripheral nerves, or of their associated peripheral neurons, as manifested by disturbance or abolition of their functions. By thus defining multiple neuritis I exclude all cases of neuritis directly due to local traumatism or compression, but I do not exclude those in which the neuritis arises as the result of the general action of a toxin, developed locally in connection with a local lesion."

This picture is often accompanied with clear-cut evidence of dyscrinism such as has been mentioned, and benefit follows the indicated organotherapy.

79. OBESITY

Types of Obesity — Pancreatic Obesity — Thyroid Obesity — Pituitary Obesity — The Gonad Factors — Obesity Essentially a Pluriglandular Condition — Diagnosis and Treatment — A Routine Procedure — Warnings Are in Order — Adiposis Dolorosa.

AN EDITORIAL in the *Medical World* (London, April 3, 1931, xxxiv, p. 116) contains some "New Views about Obesity" that may serve as a suitable introduction to our consideration of this important and thoroughly difficult subject:

"Were we asked to name the most troublous ailment that the general practitioner has to treat, we should be inclined to say—obesity. Always a horror to the woman who declines to accept *fat, fair,* and *forty* as synonymous, now that the slimming epidemic has attacked her daughter, the G. P. has two patients where he had only one. And yet the problem of reduction is, or should be, just a matter of balancing the supply and demand of the organism. The *Journal of the American Medical Association,* in a critical consideration of obesity, puts the aim as the depletion of the fat (or energy) reserve by so reducing the energy intake that the exigencies of metabolism quite consume the stores to meet current needs. And the process is accelerated by expanding the demand for energy by increasing the work done; hence muscular exercise is the first and greatest factor in reduction. The whole process the *Journal* sees as one of physiological bookkeeping, and common exogenously caused obesity might be easy to tackle were it not that the cases where lessened energy intake actually leads to a gain in weight point to an endogenous cause, *i.e.,* a dysfunction of the omnipotent endocrines. Moreover, research proves that the water balance must be taken into account also. This confirms German experience that drinking while at meals increases the appetite and so (indirectly) the weight, especially if a salt-free diet is not adopted. So we arrive at the result that the ingestion of fluid by simple storage, may increase the weight even though the body tissue is consumed. Plain hints for success in treatment."

Now that thousands of obese persons are turning to beauty specialists rather than to physicians, the profession is taking considerably more interest in the subject. Medical men know that obesity is far more than an esthetic problem, and that it takes something more than a reduced diet and a muscle vibrator to control it. Of course, obesity is not merely a matter of pounds. It is a question of physical and physiological well-being and normal body metabolism. Some persons are at par when they appear to be too heavy; and the reverse is just as true. For this reason, it is not sufficient for us merely to advise our patients that they should weigh so much because they happen to be a certain height.

TYPES OF OBESITY—There are two principal types of obesity: the endogenous, due to chemical changes within the organism; and the exogenous, usually due to circumstances arising outside the organism, such as overeating and under-exercising. There is much misunderstanding about this subject, and the consecutive reading of a dozen recent papers leaves one dazed. For example, the famous Julius Bauer, of the Allgemeine Poliklinik, in Vienna, and S. Silver, of New York, in discussing "Obesity, Constitutional or Endocrine?" (*Am. Jour. Med. Sc.,* June, 1931, clxxxi, p. 769), emphasize the essentially constitutional character of obesity. In the summary of this interesting article they say:

"Endocrine obesity exists, to be sure, but obesity resulting from demonstrable endocrine dysfunction is uncommon (some 3 per cent. of the cases studied).

"We wish to insist that, although there may be other causes for obesity, the *usual* one is to be found in the constitutional make-up of the individual and not in exogenous factors."

Evidently "constitution" means something different to these writers from what it does to some of the rest of us. It seems to me that "the constitutional make-up of the individual" is endocrine from beginning to end; and there are scores of authors with similar views.

However, the metabolism of growth is not under the jurisdiction of any single secretion. The subtle government of the body economy, being too democratic, in this as in most of its other processes, seldom yields to the domination of one gland. First in importance are the thyroid, the pituitary, and the sex glands; next, the adrenals, the pancreas, and the thymus.

We are accustomed to hear of particular gland types of obesity, such as thyroid obesity or pituitary obesity, but the conviction is growing among clinicians and investigators everywhere that no one gland can be incriminated by itself. T. Christiansen, of Odense, Denmark (*Endocrinology,* March-April, 1929, xiii, p. 149), while discussing a dysendocrine syndrome called *macrosomia adiposa congenita,* which depends on a hyperfunction of the adrenal cortex (Apert), said that "most likely macrosomia—as well as the suprarenal syndromes on the whole—is a pluriglandular syndrome." Louis Cohen, of St. Louis (*Bull. St. Louis Med. Soc.,* Feb. 14, 1929, xxiii, p. 281), referring to the particular glandular types of obesity, remarked that "a combination and fusion of any two or of all three types is the usual condition encountered in adult life." Such opinions could be multiplied ad infinitum. For instance, Leonard Williams, of London, in his clever and instructive work, "Obesity" (London, Oxford University Press, 1926, p. 52), said:

"Since we have learned that sugar tolerance is a question in which the endocrine system generally, and the pituitary in particular, is deeply concerned, no explanation which confines itself to the pancreas can be regarded as wholly satisfactory."

Williams might well have added that no explanation of any endocrine phenomenon is wholly satisfactory when it confines itself to one gland. However, while remembering the eternal interactivity of hormonic influences, it is also important to discover the chief mischief-makers. Usually there is a ringleader whose influence predominates, more or less, and this is the virtue in a gland-type classification of obesity. We adopt the method also for the reason that such a classification is simple and obvious, though it carries with it the danger of helping beginners into the illusion that the problem is too simple, too uniglandular.

Since diabetics form such a large percentage of the obese population, we shall start with the pancreas.

PANCREATIC OBESITY—A new term has sprung up in current literature—"pancreagenetic obesity." E. P. Joslin, of Boston ("The Treatment of Diabetes Mellitus," Philadelphia, Lea & Febiger, 1923, p. 140), considers diabetes a penalty of obesity; and, the greater the obesity, the more liable is nature to enforce the penalty. Obesity, he believes, is usually an acquired characteristic, and acquired characteristics are little subject to transmission from parent to child. In an analysis of 1063 cases, Joslin found that obesity preceded the onset of diabetes in no less than 40 per cent. In his opinion:

"The fashion-plate makers are far ahead of insurance company presidents in their propaganda for a normal weight, and the figures portrayed in the fashion magazines might well bear the legend, 'Immune to Diabetes.'"

There may be little authority for saying that a very rich diet is directly responsible for diabetes; nevertheless, this disease occurs with such frequency in overeaters among the wealthy and middle-aged, that this etiological factor is worth considering. And, since the pancreas is also concerned with the metabolism of fats, the plausible cause of diabetic obesity shifts from exogenous to endogenous, for it is very likely that the pancreas, after being imposed upon year after year, eventually gets tired of putting in so much overtime and gradually allows some of its duties to accumulate—in the way of excess body weight.

This fat-producing mechanism, with its "wheel within a wheel," has been described clearly by Leonard Williams, also by Wilhelm Falta, of Vienna. Williams (*loc. cit.*, p. 94) puts it this way:

"Of overaction among the catabolic endocrines, we recognize Graves' disease and acromegaly, and among the anabolic endocrines, pancreagenetic obesity. . . . If we bear in mind the essentially chemical nature of the endocrine activities, it is easy to understand that one of the principal functions of the hormones is the neutralization of toxins. . . . When, however, the endocrine system is jangled and out of tune, not only are endogenous toxins easily formed, but their neutralization is less prompt than it should be, so that a certain degree of toxemia ensues. . . . Anabolism enjoys undisputed sway, and the victim immediately puts on flesh."

But Falta sees the workings of this mechanism just a bit differently ("Endocrine Diseases," Philadelphia, P. Blakiston's Son & Co., 1923, p. 584):

"We can conceive, however, that the origin of obesity may receive an impetus through a primarily strengthened (or stimulated) function of the insular apparatus, in that the assimilation of larger amounts of food goes on abnormally easily, and hence there does not occur the setting free of the reactions which in normal individuals militates against the long-continued ingestion of an amount of food which is greater than the requirements."

Commenting on this particular statement by Falta, Williams said (*loc. cit.*, p. 99):

"Put shortly, this means that the pancreas, being the great anabolic endocrine gland, its stimulation leads to increased anabolism and consequently to obesity."

THYROID OBESITY—In considering endocrine obesity, one usually thinks of the thyroid first because so very many cases of increased weight are due to mild hypothyroidism, or *myxédème fruste,* as Eugene Hertoghe, of Antwerp, first called this common functional disorder. Thyroid obesity and distinct myxedema are not the same, however. Because of the suboxidation resulting from an insufficient production of the thyroid hormone, the patient can accumulate weight without showing the prevailing skin symptoms or the mental sluggishness of myxedema. Some authors claim that thyroid obesity is due not so much to fatty deposits as to infiltration of mucin and other principles in the tissues throughout the body, conforming more nearly to the literal meaning of the word *myx-edema.* Most of the excess tissue in true myxedema is not really fat. The tendency to the minor forms of hypothyroidism, as a result of infectious disease or toxemia that overworks the thyroid, may develop into something worse; and the reduced oxidation eventually involves the associated glands, particularly the pituitary and the ovaries, and the patient actually has a pluriglandular hypocrinism.

The most striking thyroid obesities are in young girls and in women at the climacteric (myxedema, indeed, is almost exclusively a climacteric dis-

ease). In both conditions, the thyroid is the gland chiefly concerned, though the ovaries are important accomplices. Because of its evident "pluriglandularity," the subject is discussed under that subhead later in this chapter.

PITUITARY OBESITY—Classical pituitary obesity is interpreted as a hormonic sign of posterior lobe insufficiency. In Tice's "Practice of Medicine" (Vol. VIII, pp. 464-484), William Engelbach and J. L. Tierney, of St. Louis, assert that its character and location suggest secondary gonad insufficiency as its origin, because this frequently accompanies the bilobar cases. On the other hand, an argument against the gonad etiology is that, in the pure anterior lobe insufficiency, there is complete aplasia and absence of function of the gonads. Harvey Cushing, of Harvard, believes that typhoid fever is either a predisposing or an exciting cause of pituitary disease. The obesity that occasionally follows typhoid, therefore, may be caused essentially by an insufficiency of the posterior lobe.

Some authorities assert that the pituitary obesity of children (usually developing after the fourth or fifth year), is due to posterior lobe insufficiency, while the disease in adults is attributable to a deficiency of both lobes, and develops in the early twenties. Considerable research, however, shows that it is difficult to maintain this position. Engelbach says that 60 per cent. of juvenile obesities are attributable to hypopituitarism, although adults are not immune.

The anterior lobe of the pituitary produces the growth stimulant, but removal of this lobe from dogs causes adiposity. Any decrease in posterior lobe activity results in a very high tolerance for sugar and an accumulation of fat, particularly on the abdomen. There may be considerable mammary enlargement, with dangerous deposits of fat in the mediastinum and the pericardium. The so-called "girdle type" of obesity, in which there are heavy deposits of fat upon the abdomen and thighs, is now conceded to be predominantly pituitary in origin.

The well-known Fröhlich syndrome, or dystrophia adiposogenitalis, is caused by an insufficiency of the anterior as well as the posterior lobe. Sixty cases showing this syndrome were selected by A. Gardiner-Hill, I. Jones, and J. Forest Smith, of London (*Quart. Jour. Med.*, April, 1925, xviii, p. 309), who found that about one-third dated from birth and that 60 per cent. were due to subsequent illness. The sella turcica was found to be abnormally small in 60 per cent. They believe that in many of these cases there is first a state of hyperpituitarism, and, later, one in which hypopituitarism predominates.

It is very difficult to set down an inflexible record of the clinical findings in pituitary obesity. Engelbach and Tierney report a case of preadolescent pituitary obesity in a young man as attributable to a hyposecretion of both lobes. The basis for this follows:

1. *Anterior lobe* involvement causing arrested skeletal development; short long bones; small hands, head, and acral bones; also there was aplasia of the genitalia.

2. *Posterior lobe* involvement with a history of sudden, rapid gain in weight. Clinical girdle and mons adiposity. High sugar tolerance.

3. *Aneoplastic type,* for there was a small sella turcica and absence of the signs of pituitary neighborhood intracranial pressure. (For a further consideration of pituitary symptomatology, see Chapter 30.)

THE GONAD FACTORS—Three-fourths of all cases of endocrine obesity are found in women. While many of these are attributable mainly to ovarian dysfunction, others—and these form a large share—are directly related to the thyroid function. This is not surprising when we remember that dysovarism often stresses the thyroid, or the pituitary, or both.

The very common problem of climacteric obesity is, of course, a pluriglandular one, involving the ovaries, the thyroid, and the pituitary. Speaking of it, Leonard Williams says (*loc. cit.,* p. 84):

"It matters little whether the disappearance of the ovarian tribute acts on the one hand via the thyroid, or the pituitary, or both; or, on the other, by a direct influence on all the body cells through the blood stream. The fact remains that coincidentally with the cessation of this side of ovarian activity, the body temperature falls. It falls gradually, it remains low, often as low as 96° F. for a considerable period, and then tends slowly to rise again. . . . The fact of this lowered body temperature means diminished combustion, and diminished combustion (on the same intake) means an increased storage of fat."

Why do some girls become fat at or near puberty? Why does obesity occur in one member of a family and not in another? Is there not some relationship between obesity and goitre? Why is obesity in girls and young women (and in older women, too) so often connected with menstrual irregularities?

In answer to these questions, I have submitted the thesis (*Med. Jour. and Rec.,* June 5, 1929, cxxix, p. 620) that thyroid stress is the chief cause of obesity in girls, even though it may be shown conclusively in a given case that it is no longer an outstanding feature, and even though thyroid therapy may fail to render any notable change in the weight and general conditions. One frequently meets the obese girl whose history shows the following

sequence of events: (1) prepuberal stress from infections and toxemias (tonsillitis or influenza); (2) the development of a goitre; (3) delay of the onset of puberty and the subsequent irregularity of menstruation; (4) the coincident disturbance of fat metabolism. When such a patient is treated as a thyroid case rather than as an ovarian one, there usually follows the simultaneous regulation of the goitre, the menses, and the obesity. Goitre in girls may result from infective conditions—exanthemata, infections of the lungs, and foci of infection. This gives us a partial explanation of the obesity as well as of the goitre. Suffice it to say that stress at or near puberty may upset *all* the thyroid functions, reducing its detoxicative powers, its metabolic efficiency, its ovarian-regulative capacity, its regulation of the mental acuity and powers, its control over the nutrition and reactivity of the skin, and, most important of all, its maintenance of the endocrine balance. Louis Klein's comments on this subject (*Therap. Notes,* July-Aug., 1921, xxviii, p. 51) are as follows:

"The gonads act as stimulators or activators of the general cell chemistry. Deficiency in ovarian or testicular internal secretion leads to sluggishness of the ultimate body cells with consequent incomplete oxidation and elimination of waste products. The obesity of the eunuch is a splendid example of the result following the sudden deprivation of testicular secretion. Other examples of gonad obesity in the young are cases of sexual infantilism with undeveloped and imperfectly functioning ovaries or testes."

OBESITY ESSENTIALLY A PLURIGLANDULAR CONDITION—From the study of several thousand cases, I am convinced that true thyroid obesity is practically never found uncomplicated, and that a true ovarian type of obesity per se is an impossibility. The explanation is that the physiological harmony of the endocrine glands is so balanced that one cannot have a condition in which, for example, the thyroid is likely to cause a marked change in the oxidation and chemistry of the body without at the same time affecting the other associated glands. Therefore, in the presence of hypothyroidism, there is practically always an associated dyspituitarism. On the other hand, a well-defined pituitary insufficiency eventually involves the thyroid by thrusting added duties upon it.

Exactly the same thing occurs in the ovarian or climacteric forms of obesity. The ovaries are dependent upon both the thyroid and the pituitary for hormone stimuli; hypothyroidism has been shown to be a very common cause of ovarian dysfunction, and hypopituitarism invariably is associated with functional ovarian insufficiency. These are vital points in the treatment of many cases of obesity.

DIAGNOSIS AND TREATMENT—From the standpoint of differential diagnosis, a number of test measures are helpful. In cases of distinct thyroid deficiency, the basal metabolism is low. The therapeutic use of thyroid, which comprises the basis of my Thyroid Function Test (31), is of equal value in determining real thyroid apathy. Distinct hypopituitary cases almost invariably show an increased carbohydrate tolerance, which is easily demonstrated in any clinical laboratory. Of course, both these types—the thyroid and the pituitary—may show marked sex gland disturbances; but, since it has never been proved that gonad obesity occurs alone, irregularities such as amenorrhea and asexualism should not complicate the diagnosis.

Before outlining my own regular procedures in treating obesity, reference is made to the work of others. H. Gardiner-Hill, of London (*Jour. Obst. and Gynæc. Brit. Emp.*, Summer, 1930, xxxvii, p. 256), believes that a beneficial effect on obesity and on carbohydrate metabolism can be expected from the oral administration of thyroid and whole-gland pituitary. He uses desiccated extracts, given in gradually increased doses, starting with ½ gr. of each a day and working up to a point where the patient loses one or two pounds a week. Estimations of the sugar tolerance are made at frequent intervals to control the dosage. Gardiner-Hill, Jones, and Smith report satisfactory results from the treatment of sixty cases of the Fröhlich type, with a combination of thyroid and whole pituitary.

Among his counterchecks, Leonard Williams suggests that, when giving thyroid to a patient for the first time, it is well to add about 1/20 gr. of parathyroid and a suitable amount of iodine to each dose of thyroid. He says (*loc. cit.*, p. 149):

"In the case of the thyroid, its therapeutic association with another gland will often bring about the success which is denied to the thyroid alone. In my experience [in the treatment of obesity] the most fruitful combination has been thyroid plus pituitary."

Williams advises persistence in cases demanding pituitary therapy. He uses whole gland by mouth, often pushing the dosage to 30 gr. t.i.d. for several weeks. Whole-gland pituitary extract is most satisfactory in treating young patients; but, when results are not forthcoming, he combines with it a small dose of thyroid. "This, however, should be done with very special caution, because people who are deficient in pituitary very quickly display intolerance to thyroid."

This eminent Harley Street specialist continues:

"It is generally agreed among clinicians that the administration of gonad extracts by the mouth is very seldom followed by satisfactory results. Of the pure extracts, whether the testis or ovary, I think this is true, although

I can gladly testify to having obtained considerable satisfaction from the pluriglandular preparations in which these extracts figure, which are supplied according to Harrower's formula."

In treating obesity in children whose basal metabolic rate is 5 per cent. below normal, Gregorio Marañón, of Madrid, always gives thyroid extract; but he suggests that girls should receive ovarian extract also.

In their monograph, from which a quotation already has been made, Engelbach and Tierney warn us not to give too much encouragement for the glandular treatment of obesity. Organotherapy should consist of large doses of desiccated anterior and posterior pituitary substances by mouth, combined with intramuscular injections of the corresponding extracts. While pituitary extracts alone fail to produce any change in symptoms, according to the observation of these workers, pituitary, thyroid, and ovarian extracts produced very marked amelioration of all constitutional symptoms such as headache, fainting spells, thoracic pressure, abdominal ballooning, and amenorrhea.

Even with this routine it is impossible to accomplish lasting and satisfactory results in all cases of obesity. Some very gratifying work is now being done with shock therapy. Supplementary treatment with protein injections, such as Lactigen (Abbott), has given excellent results in some cases (105).

A remarkable instance of the by-effects of foreign-protein therapy in the treatment of obesity is described by J. St. Lorant, of Prague (*Wien. Arch. f. inn. Med.*, Dec. 10, 1924, ix, p. 341). In fourteen cases ordinary methods of reduction treatment, including thyroid and non-specific protein therapy alone, were unavailing; but, when non-specific protein injections and thyroid feeding were combined, the patients lost weight, being reduced almost to normal without restriction in diet or vigorous exercise. The injections of protein were given at intervals of three or four days. St. Lorant has shown that the organism retains nitrogen and salts during the reduction process. The loss affects only water, fats, and carbohydrates.

A ROUTINE PROCEDURE—Although, as suggested, it is not wise to classify our obese patients strictly according to certain endocrine types, there are classifications into which they automatically fall when they present themselves for treatment: the young and the middle-aged; male and female; exogenous and endogenous. In the routine handling of obese patients a thorough examination is advisable, first eliminating all the exogenous factors if possible. If there are any dietary errors, or a tendency to bulimia, the appetite must be curbed and the patient put on an accurate caloric diet. Appropriate exercise should be insisted upon.

In treating an obese girl of sixteen or seventeen, for example, who has a goitre and whose history has shown a prepuberal stress from infection and toxemia, with delay of the onset of puberty and irregularity of menstruation, it is advisable first to administer iodine in order to spare the thyroid and thus obviate the results of a thyroid breakdown. A routine treatment of these conditions, then, is a detoxicating, remineralizing, neutralizing regimen including thyroid extract in minute doses, iodine in some inert and slowly assimilable form (103), and alkalies (100).

For reasons already given, an obesity connected with hypovarism calls for organotherapy directed at ovarian, thyroid, and pituitary insufficiency. Many a case in which organotherapy, previously consisting of either thyroid, or pituitary, or corpus luteum, was changed for a pluriglandular therapy containing all three of these preparations, has shown immediate betterment—first, in the general feelings; secondly, in the menstrual manifestations; and, finally and to a lesser degree, in the obesity itself.

In these cases of pluriglandular dysfunction, the formula of choice is a combination of thyroid, pituitary, and ovarian substances known as Gonad-Ovarian Co.* The dosage is 1 tablet, q.i.d. When menstrual disorders are also present, it is advisable to follow the cyclic method of dosage. If the patient is menstruating or if there is a molimen, prescribe 1, t.i.d., a.c., for fourteen days; double the dose for from seven to ten days before menses (or molimen); omit for a week at onset of menses; repeat. This may be augmented later by single doses of thyroid or pituitary, as the case may be.

These endocrine products are given in what is really a diagnostic way. When conditions are fairly stable, and the previous pluriglandular treatment has appeared to accomplish its maximum effect—say, after two or three months—*in addition to the previous routine dosage,* prescribe Endothyrin* (gr. ½) once a day for a week or even longer. This dose is doubled for another week or more, then trebled similarly, and finally omitted for a week or more. The same procedure may be carried out with the formula, Pituitary Co.,* which contains large doses of total pituitary and anterior lobe, each tablet representing the equivalent of 18 gr. of fresh gland, half of each. Give one sanitablet four times a day for a week, double the dose for the next week, treble it for the third week, and so on. The idea is to note the acceptability of, or tolerance to, these varying doses. During this prolonged period, the patient is kept under fairly close supervision, and records are kept for later comparison. The response of the patient to these varying stimuli may be of decided therapeutic value, but it may also be of equal or even greater diagnostic advantage.

WARNINGS ARE IN ORDER—A warning must be recorded here against the administration of thyroid, or any other form of organotherapy, without close medical supervision. Too often patients start treatment, begin to get some benefit, discharge the doctor, and proceed with their treatment unchecked. It is dangerous. I have seen several patients who previously had been under the care of renowned specialists in San Francisco and Santa Barbara, and who "were ready to jump out of their skins" from thyroidism. They had not been warned sufficiently that enough thyroid to burn up several pounds of fat a month would soon be too much of a good thing.

Another warning has to do with the diet: One cannot treat an endocrine obesity with endocrine therapy alone. Obviously a 200-pounder has to eat for a person of that weight, yet theoretically he should eat only for a person of his ideal weight, or less. Practically all these patients eat far too much, as evidenced by the frequency of high sugar tolerance and a liking for sweets.

The ideal treatment of obesity is a thoroughgoing one—directed at each factor, fitted together with individuality, and persisted in indefinitely. In the Appendix (102) will be found some helpful points about dietary care.

ADIPOSIS DOLOROSA—Something must be said about a strange form of adiposity known as Dercum's disease. It was in 1892 that the Philadelphia neurologist, F. X. Dercum, described a peculiar disorder in which there appear in various parts of the body localized deposits of fat in tumor-like form, which are tender and often painful. This condition, sometimes called lipomatosis, for years was erroneously considered to be a nervous disease. It is not merely a development of fatty growths, but of *painful* fatty growths. Further, adiposis dolorosa is clearly a systemic difficulty with the fat deposits as incidents in its progress. Other symptoms are a marked degree of asthenia, muscular aches and pains of a rheumatic character, as well as evidences of both functional and (at autopsy) structural damage to the thyroid and sometimes to the pituitary.

It is not yet determined whether the endocrine features are cause or effect, nor can it be stated whether the undoubted nerve changes are the result of endocrine disease or merely associated with it.

Dercum's disease does not respond well to treatment, although thyroid therapy is in order. The fact that it is much more common in women, and especially at the time of the menopause, prompts the consideration of its treatment as a climacteric manifestation.

Surgery has been advised and, of course, circumscribed and structurally suitable growths can be removed; but this has no effect on the general symptoms.

80. OVARIAN DYSFUNCTION

Amenorrhea — Delayed Puberty — Dysmenorrhea — The Picture of Dysovarism—Frigidity—Infantilism—The Menopause—Menorrhagia and Mammary Therapy — Menorrhagia in Girls — Metrorrhagia — "Mittelschmerz"—Ovarian Irritability—Ovarian Poisoning—Premature Senility in Women—Treatment of Dysovarism.

EVERY FOURTH civilized woman, so it is said, has in varying degree a periodic syndrome of functional, nervous, circulatory, and menstrual disorder. This probably is no exaggeration of the frequency of ovarian dysfunction, and it manifests itself in many different ways, simple and serious.

Before we consider the symptoms and treatment of dysovarism, let us establish firmly the point of view from which this subject may be most satisfactorily viewed.

"A woman is a woman because of her internal secretions." This aphorism, the origin of which I cannot trace,† expresses an idea that has revolutionized our conceptions of gynecology. Before the hormones were known, what we now call dysovarism was a problem hidden in mystery, and the clinical recommendations of medical writers of past years now seem quite absurd. However, the remarkable developments in our knowledge of endocrinology have enabled us to explain the hormone character of certain stimuli and the resulting responses, and at the same time have suggested means whereby these functions may often be modified effectively.

Serious variations in ovarian hormone production can and do occur (11), and by means of organotherapy it is possible to augment the insufficiencies and, in a degree, overrule the excesses. But still greater accomplishments are now possible because of our knowledge of the close relationship of the other endocrine glands that control the ovarian functions, especially the thyroid, pituitary, and adrenals.

The whole story is too long to tell in detail here, but the essential information may be condensed as follows:

AMENORRHEA—Absence of menstruation when it normally should be present is properly called "amenorrhea," but the term is commonly applied to menstrual insufficiencies, delays, and irregularities, which more exactly should be called "oligomenorrhea" or scanty menstruation. (The Germans also differentiate infrequent menstruation, calling it "opsomenorrhea.")

†I am told that it was Rudolf Virchow, the German pathologist, who once said: *"Mulier est quod est propter ovaria sua."*

Besides considering the menstrual variations, we must think of amenorrhea etiologically, for the success of our treatment depends largely upon an accurate estimation of the underlying cause.

Uterine Amenorrhea is practically always due to utero-ovarian hypoplasia and other manifestations often associated with infantilism (58). It is more organic in character than other types of amenorrhea, yet so potent are some of the newer endocrine measures that hypoplasia of ultimate degree with sterility and complete amenorrhea of years' standing has been made to respond to organotherapy. This ultimate type of amenorrhea is considered further as a uterine disorder with sterility (96).

Ovarian Amenorrhea is an essential form of ovarian insufficiency due to (1) castration, (2) atrophy, and (3) essential or inherent ovarian insufficiency. There is also an anomaly due to congenital absence of the ovaries. Castration is no longer so common as it used to be, but in its place we find a corresponding condition due to X-ray or radium therapy. Essential hypovarism is also rare, for the majority of cases are really secondary to other endocrine defects, especially of the thyroid and anterior pituitary. One of the chief types of true essential amenorrhea is that which is called "suppression of the menses." It follows ill-advised cold baths, prolonged exposure in cold, wet weather, etc. Here the difficulty is peculiarly ovarian, and treatment is expectant.

Constitutional Amenorrhea is not solely an ovarian matter. The state of intense anxiety into which some women throw themselves each month may give place at times to a definite neurasthenia or psychasthenia with amenorrhea. Such a dyscrinism includes far more than the ovaries themselves. As W. P. Graves says in his "Gynecology" (Philadelphia, W. B. Saunders Co., 1929, p. 692):

"Under the term 'functional amenorrhea' are classed such cases of temporary cessation of the menses or delayed menarche as are not related to any definite pathology. One of the commonest causes of functional amenorrhea is some sudden psychic emotion, especially that of fear or anger. . . .

"Anxiety from fear of pregnancy, or from great desire to have children, may delay the period for days or even months. In the latter case, motions of a child may be imagined and there may be apparent enlargement of the abdomen, the so-called 'phantom pregnancy.'"

In these quite numerous cases we must attempt to curb the emotional tendencies, stabilize the sympathetico-endocrine mechanism—neither of which is an easy matter—and at the same time treat the amenorrhea not as hypovarism alone but as the much more common disturbance involving the ovarian trinity—thyroid, ovaries, and pituitary (see page 555).

DELAYED PUBERTY—The initiation of ovarian function and the establishment of reproductive activity, or maturity, is the first of the two critical periods in a woman's life. At this time there is an unusual strain on the endocrines, especially the initiators and regulators of the ovarian activities—the pituitary and the thyroid.

In the consideration of goitre in girls (57) an attempt has been made to explain how this condition comes about so commonly at puberty. The argument will not be repeated, except to say that the stress of this period may suffice to cause not only goitre but obesity, and also to initiate fundamental ovarian abnormalities. One of these defects is a delay in the establishment of menstruation, frequently noted after a severe illness or shock or even after a change of environment. Sometimes these girls are seemingly normal, except that the menses have not appeared at fifteen or sixteen; or there may have been an attempt at a flow and then none for a year or more.

What shall we do in such cases? This is an oft-repeated query, the answer to which depends entirely upon the picture as a whole—not upon the supposed amenorrhea alone. Usually, I reassure the parents and pass the matter off lightly by saying that some girls menstruate early and others late, and that the menses will start in due time. But, when the amenorrhea is accompanied with mental peculiarities, when the girl is not physically developed, or there is something lacking in the way of feminine outfolding, it is time to act. Strange things happen when the endocrines are not functioning harmoniously, and any evidence of such discord should serve as a warning. Dementia præcox not infrequently seems to arise upon this very foundation.

My rule is to ignore delays of two or even three years from the norm of thirteen, provided there are no other symptoms—no goitre, no obesity—and that there are normal bust development, hair distribution, evidence of girlishness, and a proper school status. However, something needs to be done at once when the amenorrhea is accompanied with any one or more of the following: (1) a small goitre, (2) a moderate increase in weight, (3) a lack of axillary and pubic hair, (4) negligible growth of the breasts, (5) temperamental peculiarities, (6) educational shortcomings, or (7) dermatoses, especially acne. The treatment usually consists of an attempt to regulate the regulators first: thyroid and iodine (57), a consideration of the other causes of the increased weight (79), pituitary treatment of clear developmental defects of this nature (83), and general endocrine encouragement in the hypotonic, hypoplastic, and hypocrine cases (65). The presence of acne may be the only other evidence of the latent dyscrinism in these cases, but it is distressingly common (50).

A fluoroscopic examination should be made when there is asthma or any other suggestion of persistent thymus (93). This important possibility is often overlooked. All the evidence goes to show that the thymus is an opponent of sexual development, and, when it persists, its influence may interfere with the customary initiation of the ovarian cycle.

Among those who believe that the thymus definitely inhibits the sex glands is G. Y. Oliver, of London (*Prescriber,* Feb., 1924, xviii, p. 68), who says:

"The thymus up to the age of puberty appears to keep the gonads in check, an action of greater importance in the female than in the male. . . . From personal observation I am of the opinion that the two glands which dominate and control the ovarian stroma are the anterior pituitary and the thymus. Having proved that it is possible to cause development of the reproductive organs by means of anterior pituitary, we are confronted with the question of how to inhibit them. . . . Now if thymus can control the ovaries in acne, it ought also to do so in dysmenorrhea, which is due to ovarian overactivity."

Oliver then reports a case that illustrates his theory, and remarks: "It will be seen that it is possible to use anterior pituitary to develop the gonads, and thymus to restrain their activity."

If mental retardation is prominent, I know of nothing better than to consider these girls in exactly the same way as the backward child suffering from dyscrinism (46).

Finally, these numerous investigations having been made, and the case having been diagnosed satisfactorily as merely delayed puberty, I treat the girl for ordinary amenorrhea, advising thyro-ovarian treatment for a minimum of six months, as outlined on page 555, except that the absence of the menses makes impossible the cyclic method of dosage. However, as soon as a molimen or the merest show is seen, it is recorded on the calendar in order to push the pluriglandular encouragement at the periods when such support will be most helpful. The treatment should be continued for two or three periods after the menstruation seems to be properly started.

A word here about an exaggerated picture of this same character—extremely delayed puberty without pelvic anomaly, with, for instance, no sign of menstruation at the age of twenty-six. The problem is similar to delayed puberty in young girls, but obviously much more difficult. The treatment also is the same, but the need for persistence is so much the greater. Parenthetically, the young woman of twenty-six referred to above, began to menstruate just eight months after my effort started. Needless to add, this was not the first time she had been given organotherapy, but it did not happen to be an aggressive, pluriglandular therapy!

DYSMENORRHEA—By dysmenorrhea is meant abnormal menstrual pain.

Painless menstruation is so unusual as to be exceptional in civilized women. It is quite rare to find menstruation attended with no discomfort save, of course, the flow itself.

Endocrine Aspects—In tracing the endocrine etiology of dysmenorrhea, one first meets the ovaries; next, the thyroid or pituitary, or both; then more distantly related glands; and, sooner or later, the vegetative nervous system (91). The last is most important. W. V. P. Garretson, of New York (*New York Med. Jour.,* July 6, 1921, cxiv, p. 35), has discussed this aspect of the subject very fully. The perfect functional balance of the vegetative nervous system, he says, is dependent upon a proper hormone balance, and there is an interrelationship between both, as well as between all glands of internal secretion. He proceeds:

"The vegetative nervous system may be likened schematically to a finely poised balance beam resting on a pivotal support suspended from thyroid to ovary in the female or testicle in the male, the plane of the pivotal point being heightened or lowered as hyperfunction or hypofunction of these reciprocal glands may occur."

The left half of this balance is the sympathetic portion of the vegetative nervous system, and the right half is the parasympathetic or bulbosacral portion. Stimulation of the thyroid, adrenals, and pituitary by the introduction of the ovarian secretion, so Garretson explains, may serve to upset the balance of the vegetative nervous system, resulting in psychical and physical symptoms. He then calls attention to a point that I have emphasized persistently for the last fifteen years, namely, that in girls with inherently deficient ovaries there is a compensatory strain placed upon the thyroid and pituitary, as well as upon the adrenals. The gland that dominates the individual's physiology is the first to manifest the strain. However, if the strain is prolonged, the entire chain may break. In his consideration of dysmenorrhea, this same author states that "upon these deductions depend the therapeutic indications."

An interesting observation was made by Leonard G. Phillips, of London (*Brit. Med. Jour.,* Sept. 27, 1924, ii, p. 563), regarding the frequency with which sterility accompanies dysmenorrhea. He says:

"In four hundred of my cases of bad dysmenorrhea, one-third occurred in married women, and practically all were sterile over periods varying from three to seventeen years. There are two very suggestive facts in favour of an endocrine basis in some dysmenorrhea cases: (1) The well-known association of dysmenorrhea with sterility, a fact emphasized many years ago by Duncan; (2) the remarkable success of organotherapy in some cases."

Attention must again be directed to the other members of the ovarian trinity. For instance, regarding the broader relations of the various glands to the ovaries, James H. Hutton, of Chicago (*Illinois Med. Jour.*, Jan., 1924, xiv, p. 37), says of the pituitary:

"The proper development of the ovary seems to depend, to some extent at least, on the functional integrity of the pituitary, especially of the anterior lobe. . . . I am much inclined to the belief that pain in the lower right quadrant, of which Engelbach speaks as a symptom of pituitary disease, is more likely due to ovarian insufficiency, although this latter condition may be secondary to and due to hypopituitarism of the anterior lobe."

Then, again, A. E. Hertzler, of Kansas City (*Am. Jour. Obst. and Gynec.*, June, 1925, ix, p. 783), connects dysmenorrhea with thyroid disorder. In order to determine the coexistence of goitre and pelvic lesions, he made notes regarding these points in one hundred consecutive patients examined in one month, limiting his observations to those types of goitre described as "interstitial." His conclusions are corroborated by the compilation of statistics of 1081 patients treated for goitre in his clinic during the previous year, three hundred of whom belonged to this group. The points noted are interesting because of the therapeutic prospect that they offer:

"1. Many young women present small goitres associated with mild degrees of thyrotoxicosis.

"2. Anatomically, these glands show changes in the colloid, inactive, acinal epithelium, and apparently an increase in the cells situated between the acini.

"3. Many of these patients have an associated dysmenorrhea without demonstrable anatomic changes in the pelvic organs.

"4. When these patients are treated in the conventional manner for their goitres, the dysmenorrhea disappears in the vast proportion of cases."

With the foregoing in mind, it is easy to see that there may be several interlocking endocrine causes for dysmenorrhea. However, the amount of pain at menstruation may depend upon a number of other factors. Chief among these are pelvic congestion and inflammation. Malformed or poorly developed genital organs are common causes. Obstruction due to uterine misplacement is not infrequent. Another important type of dysmenorrhea is that due to neuralgia. In these cases there is no pelvic pathology, but there is usually a constitutional picture of malnutrition, anemia, and a general chemical upset of the body. This causes an oversensitiveness of the utero-ovarian nerves, and the congestion incidental to the menstruation produces pain in varying degree. Neuralgic dysmenorrhea is fairly common, and often accompanies various constitutional disorders, vicious habits of eating and living, poor environment—all of which interfere seriously with any treatment.

Pelvic Congestion and Inflammation—Congestion and inflammation always cause pain, and, when the congestion is increased temporarily by the usual engorgement that occurs prior to menstruation, the distress is increased. Again, pathological conditions not infrequently occur which bring about changes in the ovarian capsule—thickening, cystic degeneration, etc.—and during the usual monthly hyperemia the stretching of this capsule may induce most severe but temporary pain. Such conditions do not lend themselves to organotherapy. In fact, ovarian therapy often aggravates them by its stimulating influence upon the pelvic circulation.

Anatomical Causes—One of the most common causes of dysmenorrhea is a structural abnormality of the uterus, especially the cervix. Stenosis of the cervix, malpositions of the uterus, and uterine polypi, all offer mechanical interference that may cause pain; so may the clot that often forms during menstruation. The forming of these clots is not normal, and their passage may even develop into a miniature labor. Chronic constipation mechanically causes menstrual difficulties of this nature, as does the sluggishness of the portal circulation, which leads also to hemorrhoids. Unfortunately, few of these conditions respond to organotherapy.

Treatment—The treatment of dysmenorrhea as a whole involves first and foremost, general hygiene, which includes rest and care of the bowels and the liver. Hot vaginal douches may be helpful, especially in dysmenorrhea due to congestion, inflammation, and stenotic conditions. The relaxing quality of the heat lessens the pain and relieves the uterine spasm. Certain drugs are useful for this purpose, notably benzyl benzoate, but the effect is temporary and not fundamentally curative. Pelvic decongestion may also be beneficial (106).

If there is a systemic endocrine irregularity such as hypothyroidism, obviously the treatment will include attention to this. If there is a defect inherent in the ovaries themselves or in the other glands that regulate the ovarian function, which causes unusual stress in the consummation of each monthly response, it is easy to see how dysmenorrhea will result and, too, how the restoration of the endocrine balance will end it. This is the form of dysmenorrhea that responds most satisfactorily to pluriglandular therapy —the same regulative treatment that is recommended in the control of amenorrhea and the climacteric (page 555), because the real difficulty in these patients is in initiating the menstruation, as a result of which there is an abnormal localized congestion that is not always relieved promptly by the onset of the flow. Where there is a tendency toward a sympatheticotonic condition (91) due to a generalized endocrine imbalance such as Garretson has referred to, this treatment sometimes may give spectacular benefit.

THE PICTURE OF DYSOVARISM—In order to see how easily attending disorders gradually erect themselves upon the foundation of dysovarism, let us visualize a typical case of moderate ovarian dysfunction.

The patient complains of uncomfortable sensations such as pelvic heaviness, vague nervous manifestations, and a feeling of general malaise of varying degree, lasting for a longer or shorter time prior to each expected menstruation. Delay, irregularity of onset, and a scant flow are customary. During the period of delay, the patient often suffers from severe colds (47); an old tonsillitis reawakens; headaches of quite decided severity are common (59); skin disorders are exaggerated (50); in fact, the patient is so tired and below par at these periods that any latent condition may become aggravated because of the temporarily lowered resistance. This is particularly true of those who are tuberculous (94), and it must be said with emphasis that the regulation of dysovarism invariably should be undertaken in all women with tuberculosis. When the menses are properly established, these troubles disappear more or less completely—until the next premenstrual delay.

Frequently this element of delay itself brings about a condition of neurasthenia, and it is easy to see why various neuroses may be found in women suffering from dysovarism. So far as the actual flow is concerned, there may be all degrees of oligomenorrhea and dysmenorrhea. In such patients, it is not the menstrual disturbance itself that counts for most, but chemical changes in the body that upset the self-regulating mechanism and pave the way for almost any symptom—from acne to insanity!

A less typical but still common picture is aptly visualized by Walter C. Alvarez, of Rochester, Minnesota, in his book, "Nervous Indigestion" (New York, Paul B. Hoeber, Inc., 1930, pp. 70, 71):

"I place in a separate group those women who show a masculine type of distribution of hair on face, breasts, abdomen, and legs and who sometimes have defective pelvic organs, painful and scanty menstruation, and sexual anesthesia. . . . For the sake of brevity, I continue to label this polyglandular defect with the term 'hypo-ovarianism.' I think it important that the gastroenterologist recognize this syndrome because so many of these women suffer from nervous indigestion, mucous colitis, and constipation. . . . These women seldom confess their real trouble unless the physician, noting the physical signs, suspects the presence of the psychic difficulties and tactfully opens the way for them to talk. I hope that some day, with the new ovarian hormones that are now being isolated and purified, we will be able to give these women real help."

When dysovarism is due to a shortage of hormones, as it is indeed in many a case, the prospect from organotherapy is just as good as it is in diabetes or any other endocrine insufficiency. This is to be considered further along.

FRIGIDITY—Asexualism in the married woman is sometimes a manifestation of hypovarism and sometimes a matter of marital maladjustment in which a psychic element predominates. Lack of libido may be relative, and due to the same class of causes as infantilism (*q.v.*) and the adiposo-genital dystrophy (83). Unless it is possible to connect this symptom with other definite evidences of hypovarism, such as oligomenorrhea and defective development of the secondary sex characteristics, or with those of a thyro-pituitary insufficiency, the prognosis depends entirely upon extra-endocrine factors and, frankly, is not good.

If, however, frigidity is but a part of a picture including some of the foregoing manifestations of dysovarism, the prospects are better. Routine treatment of the ovarian dysfunction often ameliorates the frigidity, especially when other benefits also result from the treatment. It must be added that more than one case diagnosed as lack of libido is in reality sexual hyperesthesia on the part of the husband.

INFANTILISM—In more ways than one, utero-ovarian infantilism is a form of dysovarism. The ovaries are small and poorly supplied with blood, and the most usual functional feature is manifested in (1) oligomenorrhea and (2) defects in the mental and physical outfolding, which include the secondary sex characteristics. The type of infantilism in mind—not necessarily associated with the usual external stigmata of infantilism (30)—can hardly originate in the ovaries themselves. In more than nine cases out of ten the fault is far removed: in the anterior lobe of the pituitary, in the thyroid, or even in the thymus. As hypopituitarism is the most common cause of this hypoplastic condition, just as it is responsible for the more obvious types of infantilism, the subject is considered under this heading (83).

Attention must be called here to the spectacular capacity of the recently perfected female sex hormone (11) to cause hypertrophy of the entire pelvic sex mechanism, and to the encouraging developments in the control of endocrine sterility by this means. The cure of sterility (96) in a hypoplastic case is one of the newer accomplishments in endocrinology, and this definitely solves the problem of the utero-ovarian hypoplasia.

THE MENOPAUSE—The closing of ovarian activity is called the menopause. It is to Gregorio Marañón, famous Madrid physician and politician, that we give credit for naming this period *la edad critica* (the critical age). So important does he consider the subject that he has written a 584-page book bearing that title (Madrid, Ruiz Hermanos, 1925, Second Edition; Translated by K. S. Stevens, St. Louis, C. V. Mosby Company, 1929).

The term "menopause" should be restricted to the time when menstruation ceases. It introduces or is followed by the climacteric—also called "the change of life" and "the critical age"—which in many women gives occasion for numerous distressing complaints. It is a period of transition during which a new endocrine equilibrium is established in which the ovaries have no part. The change of life may commence months and even years before the menopause itself, especially when this is established slowly and with difficulty.

The Natural Climacteric—When the reproductive life is completed and the genital organs gradually begin to atrophy, the loss of the hormone stimuli to which the body has accustomed itself for thirty or more years, very frequently causes considerable disturbance. This is overcome in the course of time, but the nervous and mental derangement may often be a serious matter. The period of readjustment through which the organism goes in accustoming itself to the loss of the ovarian hormone varies considerably in duration, the average time being two and a half years. The climacteric as a physiological process is of limited interest. The rearrangements and the retrogressive changes are well known. The usual train of pathological circumstances, however, is of vital clinical importance and well deserves more extended consideration.

To recall some of the physiological fundamentals: W. Blair Bell, of Liverpool ("The Sex Complex," London, Baillière, Tindall & Cox, 1916, p. 168), calls attention to the general supposition that the menopause occurs as the result of the gradual cessation of the ovarian secretion, resulting sooner or later in ovarian insufficiency. He believes, however, that in both the natural and the artificial menopause the severity of the symptoms depends upon the upset of the endocrine balance or correlation, upon changes in the uterus that prevent the monthly flow, and also upon "individual variability in regard to reproductive activity and to the stability of, and capacity for, readjustment in the endocrine system."

The organic changes that come with the menopause are too well known to be more than enumerated here. The ovaries cease their most obvious function and, coincidently, the control that they exert upon the nutrition and activity of the secondary sex characteristics, thus bringing about retrogressive changes in the structure of the skin, mammary glands, external genitalia, and, of course, the pelvic organs as a whole. These organic modifications usually cause little or no difficulty—it is the hormonic imbalance and sympathetic instability that cause the trouble.

The chief symptoms of the menopause are due to circulatory upset resulting, I believe, from indirect influences upon the adrenal glands and the

closely related sympathetic system. Reflex disturbances, common among which is headache, may be of circulatory origin, but they more likely are due to the pituitary dysfunction expected at this time (59)—a friendly and cooperative activity on the part of this gland that is not always best for the patient. Other circulatory manifestations are the vasomotor syndrome known as "hot flushes," and pelvic congestion which often causes menorrhagia. Nervous manifestations are usual during this period, including sensory disturbances in various parts of the body, latent or sympathetic irritability, and certain mental disorders, of which melancholia and depression are common.

Indisputable evidence that the climacteric is a pluriglandular phenomenon has convinced me that the organotherapy of its disturbances should always go beyond the attempt to lessen the effect of the physiologic ovarian insufficiency. However, ovarian therapy can substitute for a part of the material that the body has stopped producing, and this substitution certainly modifies the intensity of the upset and the wide-spread secondary reactions.

In fact, W. P. Graves, the Harvard gynecologist (*Jour. Am. Med. Assn.*, Oct. 15, 1927, lxxxix, p. 1309), says this about the value of such therapy:

"If ovarian substance is proved to be of marked value only in the single instance of treating menopausal symptoms—and in my experience it acts in this respect almost as a specific—ovarian organotherapy hardly deserves the ridicule that has been heaped upon it."

The connection between the ovaries and the associated glands, makes the other endocrine irregularities of the climacteric of even greater importance than those that are directly ovarian in character. The fine interbalance between the ovaries and the associated glands disposes to secondary endocrine irregularities, which to me are more important than the hypovarism. After all, ovarian insufficiency is inevitable and normal at the menopause; but the associated glandular disturbances may be decidedly abnormal and preventable. For this reason they acquire, in my estimation, a far greater clinical importance. To illustrate: If the thyroid knows no better than to try to reestablish the ovaries in their former endocrine activity and concerns itself to such a degree that it becomes enlarged or functionally depleted, why may not the associated work of the thyroid and its many varied offices be sadly interfered with? This undoubtedly explains the frequency with which ultimate degrees of thyroid insufficiency or myxedema are observed at the change of life. It was Oliver T. Osborne, of Yale University (*New York Med. Jour.*, Sept. 7, 1918, cviii, p. 401), who said:

"This is the period of life when myxedema is most frequent, by far the majority of all non-operative myxedematous cases occurring in women, and in the decade from forty to fifty."

Some remarkable statistics have been given elsewhere, and it is asserted that only 10 per cent. of the recorded cases of myxedema have occurred in men, while 95 per cent. of the cases of myxedema found in women were noted in the climacteric decade.

Again, obesity is far more common at this particular period than at any other. Evidently the thyroid, having overdone itself in a vain effort to assist the ovaries, is no longer able to keep up its normal metabolic speed, as proved by the basal metabolic test, the cellular infiltration, and the generally defective oxidation (79).

Naturally, the symptoms associated with the climacteric vary with the patient and, no doubt, are dependent upon psychic as well as physical factors. Blair Bell (*loc. cit.*) classifies the chief types of climacteric phenomena as psychic, vasomotor, general metabolic, and gross changes in the endocrine and mammary glands. The endocrines, he believes, exert a regulating effect on the vasomotor system:

"Behind these direct effects of the internal secretions in regard to the vasomotor system are the indirect results brought about through the general metabolism. For instance, the calcium metabolism is directly influenced by most of the internal secretions. . . . When insufficiency of the ovarian secretion is brought about either naturally or artificially, all the other endocrine organs of the body are also affected, and as a result vasomotor symptoms are commonly seen. . . . These metabolic derangements play an important part in the psychical disturbances and alterations which so frequently occur at the menopause."

These psychic reactions may dwarf all other symptoms. They may be simple and fleeting, and again they may be most complex and permanent. In my opinion, the principal cause of the nervous breakdown at this time of life is preeminently an endocrine one. More serious mental upsets occur quite frequently; in fact, there is an unpleasantly large incidence of insanity in women at this period (see page 497).

In his "Principles of Therapeutics" (Philadelphia, W. B. Saunders Co., 1921, pp. 479, 484), Oliver T. Osborne makes this statement:

". . . a too rapid cessation of ovarian activity at the time of the menopause may cause physical debility, mental depression, and even melancholia. . . . When the right combination or the right glandular extract is found and given, the improvement in the patient is sometimes phenomenal. Digestive disturbances, headaches, and dysmenorrhea disappear, and the whole mental and physical condition of the patient is improved."

It is fortunate, however, that the neurotic and psychic imbalance of the menopause, despite their apparent seriousness, may respond to the restoration of the endocrine balance far better than do seemingly less serious mental

disorders where the endocrines seem normal. There is more about neurasthenia as an endocrine syndrome in a separate chapter (77), and some additional data are given about mental disorders, including some encouraging experiences from a large mental hospital in the Irish Free State (71).

The Artificial Menopause—There are two forms of artificial menopause, both of which are usually more serious and more difficult to treat than the normal change of life. The so-called "surgical menopause" is an eventuality that is much more rare now than when abdominal surgery was fashionable and before the endocrine value of the ovaries was properly appreciated. In place of the surgical menopause nowadays we have the "X-ray menopause" and, less frequently, the "radium menopause." Such interference is becoming quite common, but it is not so ultimately satisfactory as surgery.

While the artificial menopause may overcome serious difficulties like menorrhagia, it commonly brings with it an endocrine upset that is equally serious because of the rapid and sudden removal of the endocrine influences of the ovaries and the resulting concern manifested by the most closely related glands—the adrenals, thyroid, and pituitary.

My observation of end-results leads me to conclude that, when an artificial menopause is necessary, it is better to bring it about by surgery than by X-ray or radiotherapy. There are three reasons for this: (1) Surgery facilitates the actual removal of offending tissues; it is possible to see pelvic conditions and act accordingly. As a result (2) in a large proportion of cases, the surgery is extended to the uterus. Many times pelvic disorder is utero-ovarian, hence the surgery should be utero-ovarian. Then (3) the X-ray, in addition to its failure to eradicate the abnormal tissue, may modify it in such a way as to change the cellular functions rather than to end them. As a consequence, there may still be some endocrine function which may be decidedly abnormal. In fact, I have seen several cases in which various toxic-endocrine manifestations evidently were due to a perverted ovarian function. It is not unreasonable to suppose that the X-ray can change the cellular function as well as the structure, and occasionally the reaction to these changes may be almost as bad as the condition for which the X-ray therapy was recommended.

The artificial menopause frequently is far less responsive to treatment than the natural menopause, because (1) the ovarian loss is more sudden, (2) the absence of its hormone influences is more complete, and (3) homostimulative ovarian organotherapy has no opportunity to rearouse the waning ovarian functions and thereby lessen the concern of the associated glands.

The endocrine therapy of the artificial menopause is essentially the same

as that of the natural cessation of menstruation, except that in the presence of much sympathetic irritability, due possibly to an ovarian toxemia, sympathetic sedation (such as is frequently symptomatically effective in hyperthyroidism) may be indicated. It happens that the pluriglandular treatment of the endocrine-sympathetic upset in hyperthyroidism includes attention to the ovaries, and the formula Pancreas Co.* (63) may be substituted for the usual organotherapy of the menopause.

MENORRHAGIA AND MAMMARY THERAPY—An excessive loss of menstrual blood is known as menorrhagia. This may manifest itself in several ways, for which European gynecologists use a varying terminology: (1) *hypermenorrhea,* an increased flow at the normal time; (2) *menorrhagia,* a prolongation of a moderate flow; and (3) *polymenorrhea,* menstruation at too frequent intervals. The diagnosis depends upon the past history more than upon the immediate findings, because what is normal (in amount and frequency) for one is not normal for another. Comparisons must always be made with the patient's previous experiences.

Menorrhagia may be due (1) to mechanical causes, only one of which will be considered here—that due to hypothyroidism; (2) to constitutional causes such as syphilis, anemia, and hypocalcemia; and (3) to endocrine imbalance, as at the climacteric.

Hypothyroidism can cause menorrhagia in two distinct ways: (1) By the infiltration of the uterus and endometrium (67), thus preventing the clamping down of the uterine muscle upon the ruptured vessels—this is commonly seen in matrons and especially in myxedematous women at or near the menopause. (2) By the thyroid imbalance which, with other endocrine difficulties, brings about dysovarism with amenorrhea at one extreme and flooding at the other. This is the third of the causes enumerated above.

Not all the constitutional causes of menorrhagia are easily explained. Why should anemia cause flooding? Yet it often does, and so do tuberculosis and other forms of malnutrition. Syphilis is often directly responsible for a form of menorrhagia that is nicely controlled by antisyphilitic therapy. The most easily explained constitutional cause is that associated with defects in the coagulation of the blood, which are now connected with demineralization or calcium defects and are modifiable by parathyroid and calcium therapy.

The problems of subinvolution, metritis, and fibroids are essentially uterine rather than ovarian in character, and the subject of menorrhagia will receive additional consideration as a uterine disorder (96).

In the treatment of menorrhagia, as is the case with all other endocrine disorders, we must find and control the cause, which in this instance may

be quite remote. While this is being done, there are two interesting organotherapeutic alternatives by means of which we can lessen the pelvic congestion, the ovarian irritability (*q.v.*), and the uterine atonicity. These are: (1) the antestrous hormone from the corpus luteum and (2) mammary substance, a remarkably effective antiovarian remedy.

An article entitled "Hemorrhage from the Non-Pregnant Uterus," by Bernard Mann, of Philadelphia (*Med. Jour. and Rec.,* May 16, 1928, cxxvii, p. 548), gives some good therapeutic suggestions on this subject:

"Normal menstruation depends on a balanced secretion from the ovary and the other ductless glands, especially the pituitary and the thyroid. There has been much discussion as to what part of the ovary produces the internal secretion. It is thought that the follicle produces the substance which causes the menstrual flow, and that the corpus luteum secretes the substance which stops the flow. Theoretically, therefore, corpus luteum would be indicated in the hemorrhages due to ovarian dysfunction, but its use is usually disappointing.

"It has long been accepted that there is some relation between the menstrual function and the thyroid gland. This is shown by the increase in the size of the thyroid at the menstrual period and during pregnancy. . . . It is generally believed that cases of hyperthyroidism are associated with amenorrhea, and hypothyroidism with excessive menstruation. But there are frequent exceptions. . . .

"Bleeding due to ovarian disturbance is usually excessive; a prolonged flow at the menstrual period, with intervals of complete freedom. Later, the intervals become shorter. . . . Pituitrin will control the attack, but is not curative. Ovarian residue may be used, one ampule daily, and thyroid gland extract, 1/5 gr. three times a day."

A very definite antiovarian influence must be credited to the postulated mammary hormone, although it will be noted (14) that this active principle has not yet been isolated, demonstrated, or standardized. Nevertheless, I believe it to be an entity because the comparatively crude mammary extract does the work and has done so for thirty years.

After referring to the writings of several European authors, W. F. Von Zelinski, of Chicago (*Am. Jour. Clin. Med.,* Nov., 1916, xxiii, p. 915), says this about mammary therapy in menorrhagia:

"I am personally convinced that mammary gland is one of our best remedies for the control of hemorrhage due to ovarian dysfunction, and I believe that it is the best single remedy at our command. . . . I would lend my support to these views, even though my observations were limited to fewer cases. In my own practice, I have had most excellent results in cases of preclimacteric menorrhagia; also, in other cases of menorrhagia, of which latter I will mention one example. It is that of an unmarried woman of 32 years of age, a clear-cut case of ovarian dysfunction, with absolutely no indication of any

organic lesion or neoplasm. The patient flowed for two or three weeks at a time, at intervals of two or three weeks. All approved methods of treatment had failed; by which I mean the use of styptics and the curette. Two courses of treatment with mammary extract, for two weeks each time, relieved the trouble in a most satisfactory manner."

Henri Vignes, of Paris, several of whose comments will be found elsewhere (14), says regarding mammary therapy in menorrhagia:

"Very few of the articles written regarding mammary gland extracts are pessimistic in tone. Unsuccessful applications of this therapy, on the other hand, are not complicated by aggravations as may happen with radium or X-ray treatments, and no one has so far set himself the task of pointing out the defects of this medication."

Vignes' point regarding the comparative innocuousness of mammary therapy is well taken. It can do no harm, and it may do real good. Apparently this French writer has overlooked a brief item in the book, "Glandular Therapy" (Chicago, American Medical Association, 1925, p. 89):

"There is no clear-cut evidence to show that the administration of mammary gland preparations is of value."

The only way to settle this is by the test of trial, and this is not hard to make.

MENORRHAGIA IN GIRLS—Flooding in girls and young women is apparently a different matter from the menorrhagia just discussed. It is more essentially an ovarian disorder than a uterine one, and, because of its functional character, is not in the same category with true menorrhagia.

The flow is difficult, delayed, or abnormally spaced; and, when it does come, it comes with a rush and lasts for six, seven, or more days. It is clearly a form of dysovarism (*q.v.*). The suggestion has been made that the difficulty in establishing each menstruation causes such stress to the responsible mechanism that when the flow is actually started the endocrine pressure is too great and the job is overdone.

Because of the decided ovarian instability in these cases, ovarian support with thyroid and ovarian therapy is quite in order. Its influence extends not only to the ovaries but to the thyro-pituitary mechanism, since the endocrine principles thus added to the blood indicate to this mechanism that there is less need for undue concern, and that it may be spared some stress.

The mammary principle seems to have a steadying effect on the ovarian function, correcting uterine atonicity and pelvic congestion. The formula, Mamma-Ovary Co.,* consists of a suitable amount of mammary substance added to a thyro-ovarian combination. It is recommended for excessive menstruation in girls and young women. The cyclic method of dosage (page

555) is advised because it pushes the dose when it obviously is needed most. I confess that this procedure is based on a personal opinion for which there is little confirmation in the literature, but it is corroborated by the principles of my own hypothesis of hormone hunger (7). In spite of the criticism that "it is absurd to give antagonistic endocrine remedies to the same patient at the same time," this method is followed for the very substantial reason that it works well in the majority of cases. Sometimes the response to this treatment is much more rapid than expected, showing the catalytic nature of its effects. For instance, a physician writes:

"I want to report the good results secured in the case of my daughter who has been suffering from menorrhagia. During the first week in February I secured a supply of Mamma-Ovary Co. and began to administer it. At that time she had been menstruating for three weeks. After she had taken the tablets for a few days, the flow began to decrease and at the end of a week it had entirely stopped. Her next period was quite normal, lasting only a few days. Her general health has been greatly improved, and it seems to me that these tablets did the work very quickly."

Many an endocrine upset and its response to treatment reminds one of the pendulum. A push starts it, but it will not continue to swing unless there is some propelling power behind it. So with this idea—astonishing results sometimes occur rapidly from a single push.

METRORRHAGIA—Intermenstrual oozing or bleeding, or uterine hemorrhage after the menopause is well over, is very different from menorrhagia, and this differentiation must be sharply made. Usually metrorrhagia is not an endocrine problem, but is due to uterine disease, of which there are three fairly common types: (1) chronic endometritis, (2) fibroids, and (3) malignant disease (96).

Metrorrhagia is usually a much more serious problem than menorrhagia, and the accuracy and timeliness of the diagnosis may be a life-and-death matter. Some feel that biopsy tends to spread the disease, but its diagnostic value in metrorrhagia outweighs this possibility, especially in the presence of sinister cancer signs—anemia, cachexia, and marked loss of weight.

Radium therapy is becoming more fashionable than surgery in malignancy, but an early and thorough operation is probably the best procedure. Where this is impossible, a nagging, malodorous, irritating uterine oozing may be controlled temporarily by recourse to the decongestive organotherapy recommended in menorrhagia (*q.v.*), or by the use of Mamma-Pituitary Co.,* with or without a series of injections of the antestrin from the corpora lutea (Endoluteum,* 1 cc. daily for ten days, repeated once or more). Such treatment is symptomatic and, of course, has no real curative value whatsoever.

"MITTELSCHMERZ"—It is characteristic of metrorrhagia that the bleeding occurs outside the menstrual cycle. Not every case is as serious as the type just discussed. Some authors differentiate an intermenstrual bleeding associated with some pain, usually unilateral. This is the so-called *Mittelschmerz,* which is comparatively unimportant. George M. Gelser, of Rochester, New York (*New York State Jour. Med.,* Dec. 15, 1925, xxv, p. 1105), calls this "a rather common variation of the menstrual interval." He considers it as a reaction to the actual rupture of the graafian follicle, which may be accompanied with bleeding for one or two days in the middle of the intermenstrual period and, frequently, some abdominal pain.

The differentiation between these two types of intermenstrual bleeding is a very important matter. The minor form, *Mittelschmerz,* is temporary in character, quite regular, and unassociated with such organic disorders as myoma or other neoplasms. The response to treatment, too, is far more encouraging, as we shall now see.

Some interesting data were reported by L. M. Pierra, of Paris (*Rév. franç. de gynéc. et d'obstét.,* Jan., 1930, xxv, p. 37), who examined a series of more than one thousand women, no less than 360 of whom suffered from intermenstrual pain and discomfort. Pierra frequently found a temporary increase in the size of the ovaries and adnexa, accompanied with increased localized tenderness, and the etiology was traced to disorders of ovulation. Mammary therapy, employed for its anticongestive effect, was effective in 176 of the two hundred patients to whom it was given. Permanent relief, however, was obtained in only fifty-eight of these, whereas, in the other 118 cases the organotherapy had to be repeated each month in order to obtain relief. In the paper on "The Homology of Menstruation," by Carl G. Hartman, of Baltimore (*Jour. Am. Med. Assn.,* June 15, 1929, xcii, p. 1992), the interested reader will find some further observations based on a study of intermenstrual bleeding in the monkey.

OVARIAN IRRITABILITY, frequently known as hyperovarism, is a condition in which there is either an increase in the structure of the ovary (ovarian hyperplasia) or an increase in its circulation (ovarian congestion) and, consequently, in its functional activity. As a result of this, there may be an exaggeration of any or all of the functions with which the ovarian endocrine activity is connected.

Hyperovarism may cause extreme dysmenorrhea, due to the enlargement of the organ and the stretching of the ovarian capsule. It is also frequently a cause of menorrhagia. One of the most common types of menorrhagia due to true hyperovarism is that found in girls and young women, to which

attention already has been called. Here it seems that the whole endocrine mechanism is forced to attempt to "put it over," and there results an intense pelvic congestion, which produces a prolonged and excessive menstrual flow. Often this may occur after a preliminary period of expectancy, during which menstruation does not occur, and here a mental or nervous factor may be interjected to complicate matters. The simplest forms of ovarian irritability are those accompanied only with pelvic congestion or flooding. The treatment is that of menorrhagia (*q.v.*).

Again, hyperovarism may develop during the climacteric, despite the fact that during this time the ovarian endocrine function is expected gradually to wane and disappear. The philosophy of this condition, as I see it, is this: The body is loath to allow the cessation of so important a function, and in some subtle manner an attempt is made to refuse the inevitable demands of Nature. Undoubtedly, there is an effort on the part of the other glands to assist the ovaries to sidestep the call to retirement; and, because of these added stimuli, menorrhagia is surprisingly common at the change of life. The development of mammary therapy, however, has given us a means of controlling hyperovarism that is superior to any drug therapy—even to ergot—although, of course, certain sedative drugs may be advantageous, and hydrotherapy is distinctly helpful.

Hyperovarism may manifest itself as hypersexualism. Often the patient, ignorant of the root of the difficulty, believes her desires to be signs of original sin, lust, etc. Many a patient is so ashamed that she suffers mental and moral torture rather than discuss the matter with a physician, and the truth comes out (often incidentally and unintentionally) only after much unnecessary self-persecution and perturbation.

Erethism may be only a temporary disturbance caused by some local and self-limited ailment. If it becomes permanent and progressive, the outcome is nymphomania, a form of insanity in which all modesty, chastity, and repression of the sex impulse vanish.

Sometimes hyperovarism is part of the broad picture accompanying hyperthyroidism and is attributable to the same general type of causes—foci of infection, alimentary infection or infestation, protein sensitization, etc. Such toxemias directly irritate the ovaries as well as the thyroid; then the thyroid excess irritates the ovaries still more.

Intercourse is good for certain types of ovarian excess, but it is often impossible—at least improper. Pregnancy has been recommended, and I know of several patients in whom marriage and child-bearing ended a life of real sexual misery.

Sedatives are necessary in the treatment of hyperovarism (luminal preferably), and often a patient has been using them for some time before she presents herself for treatment. Organotherapeutic sedation is a real possibility, there being two measures well worth a trial: corpus luteum and mammary substance. The antiovarian effects of Sistomensin, Lutein, Endoluteum,* and other similar products are undoubted. Antiovarian treatment such as is directed against uterine engorgement, pelvic congestion, and menorrhagia is in order (page 556). The somewhat similar formula used in menorrhagia in girls (page 549) is contraindicated.

OVARIAN POISONING—The term *ovarische Vergiftung* (ovarian poisoning) has been used by German authors to indicate an important syndrome involving one or both of the ovaries. This difficulty is the result of pathological changes in the ovaries, and is structural rather than functional. As with other anatomical endocrinopathies—toxic goitre, pituitary neoplasm, etc.—the changes in structure cause not only an excessive production, but also a perversion, of the hormones. The result is an actual poisoning that progresses despite treatment. There are pain, congestion, and often severe and localized irritation in the pelvis, and these symptoms are accentuated by the periodic engorgement. The flow is frequently excessive and prolonged, and the resultant exsanguination and depletion seriously aggravate the picture.

Unfortunately, organotherapy ordinarily fails to control this serious dysovarism. In fact, because of its well-known circulatory influences, thyroovarian therapy actually aggravates the difficulty, increasing the pain, depletion, and congestion. Antiovarian therapy, with mammary extract and corpus luteum, may help temporarily because of its usual decongestive effect; but usually it fails. The anemia should be treated aggressively with liver therapy (40).

Surgery is indicated. The ovaries are found to be enlarged, degenerated, and thoroughly pathological, and a complete bilateral ovariectomy usually has to be performed. Recovery is rapid, but, of course, the resulting artificial menopause should be treated. Here adrenal support may be added to the other organotherapy. Adreno-Ovarian Co.* is preferable because of the marked hypoadrenal picture that has been built upon the prolonged toxemia.

PREMATURE SENILITY IN WOMEN—The loss or cessation, at the menopause, of the ovarian stimulus to the various endocrine glands eventually causes a let-down in general function, as a result of which the signs of age usually manifest themselves a little more aggressively for a time In many cases toxemias are common, the elimination is not what it used to be,

skin affections occur, and wrinkling is a special source of concern. With these symptoms comes a feeling, real or fancied, that age is creeping on.

In view of Steinach's work in Vienna (88), the possibility of accomplishing corresponding results in the female has been given much attention. Small, stimulating doses of X-ray have been used in the hope of arousing the ovaries and, through them, the endocrines as a whole. Such treatment has to be given by an expert who knows how to measure the dosage and judge the progress of the treatment. Very light exposures are required. Too often such treatment is overdone, which puts the ovarian function out of commission, and the patient is worse than if there had been no treatment at all.

Undoubtedly most of the symptoms of premature senility can be credited to the extra-ovarian endocrines, and, of all the offenders, the thyroid is probably the worst. The best method for lessening premature senility in the female is hepatobiliary encouragement (104) plus the pluriglandular treatment recommended for the mitigation of the symptoms of the menopause, to which attention is now called.

TREATMENT OF DYSOVARISM—There are two general problems to be solved in the treatment of ovarian dysfunction: (1) the ovarian insufficiencies, such as amenorrhea, infantilism, dysmenorrhea, and menopausal difficulties; and (2) the antitheses of these hypofunctional disorders, or hyperovarism, menorrhagia, etc. The treatment differs materially, as does the response, for endocrine insufficiencies respond much better to indicated treatment than do the endocrine excesses.

Hypovarism—The fundamental principle of successful therapy of the large class of ovaro-endocrine insufficiencies lies in the appreciation of the importance and the extent of the ovarian relationships.

The story of my discovery nearly twenty years ago of what was being done by Paul Dalché and his associates at the Hotel Dieu in Paris has already been recounted (page 53), so it must suffice here to reiterate the vitally important fact that hypovarism is more often due to a thyroid or a pituitary shortcoming than to any essentially ovarian defect.

The "thyro-ovarian idea," as it has been called, has completely changed the therapeutic evaluation of ovarian organotherapy. Time and again the value of ovarian extract has been decried—it has even lost the official blue ribbon of authority (1930). In many, many cases, the explanation of failures with ovarian medication is that the patients need thyroid far more than ovarian therapy. The real cause of an indisputable ovarian insufficiency is not always primarily or completely ovarian. And, even when it is, there are other doorways to ovarian stimulation besides the front entrance. This is

not an attempt to emphasize obvious differences of opinion, but a cry for a consideration of the whole patient and not just her ovaries!

The Dalché idea, which has been in extended practical use for twenty-five years, is an effort to normalize the expected endocrine imbalance in these conditions. My method is as follows: Thyro-Ovarian Co.*—thyroid, pituitary (anterior), and ovarian (total) in suitable proportions—is given in a cyclic fashion, thus: Sig. 2 tablets t.i.d. (usually a.c.) for ten days before the menses; omit for ten days at onset of menses; 1, t.i.d. until ten days before menses; repeat. This method enables us to stress these influences together and at the time when the ovaries have their greatest work to do, and to omit it when this work has been done.

Persistence is necessary to success for the reason that this type of treatment is plainly limited in the time during each month when it can accomplish most good; also because it is essentially catalytic, homostimulative, and reeducative. Treatment should be continued for three or four periods.

Three modifications of this ovarian-trinity formula are suggested for use in the long list of disorders based on ovarian dysfunction: (1) adrenal substance is added when the dysovarism is accompanied with asthenia, lassitude, and hypotension; (2) a large dose of anterior pituitary is added in the essentially ultimate types of dysovarism, such as amenorrhea of years' standing, or the pituitary type of obesity with the other commonly associated picture of pituitary-thyroid-ovarian insufficiency; and (3) thyro-ovarian oral therapy plus the same thyro-ovarian product hypodermically, or a series of injections of Plestrin,* the female sex hormone. The latter, however, is usually reserved as a trophic measure in utero-ovarian hypoplasia and endocrine sterility (96). I cannot agree that this estrin is indicated in dysovarism, and especially at the climacteric, for it is a trophic factor and has no direct effect upon extra-ovarian dyscrinisms.

Many other clinical indications and case reports by the hundred could be enumerated here, but there is space only to add that the indication for therapy in hypovarism is any functional disorder evidently due to or associated with the ovarian function, especially when that function is abnormal.

Dysmenorrhea—The organotherapy of dysmenorrhea is usually only a small part of the treatment, and differs little from that of dysovarism. In many instances the pain is only one of a series of manifestations of imbalance—sympathetic and endocrine. Hence, treatment depends upon the individual peculiarities of the case. For instance, in his book, "Troubles fonctionnels de l' appareil génital de la femme" (Paris, Masson et Cie, 1928, p. 465),

Gaston Cotte, of the Lyons Faculty, has this to say about the treatment of what he terms "primary dysmenorrhea":

"As regards medicaments, recourse will be had especially to organotherapeutic extracts, which it will almost always be necessary to employ in association. Generally speaking, if the flow has been scanty, ovarian extracts, Agomensin, thyroid or antepituitary extracts should be prescribed. If, on the contrary, there is a menorrhagic tendency, preference should be given to Sistomensin and to pituitary or mammary extracts."

Again, R. C. Hacker, of Philadelphia (*Med. Jour. and Rec.*, Sept. 2, 1931, cxxxiv, p. 246), tells of benefit from the use of Progynon tablets (11) in maximal dysmenorrhea. He gave the equivalent of 500 units prior to one menstruation and 1000 units before the next two periods with "decided improvement after the third month."

It is quite surprising to some physicians to find that they are able to remedy a serious dysmenorrhea in one case by treatment directed at hypovarism as just outlined, and in another by the opposite treatment, *e.g.*, antiovarian; yet it is being done more and more with increasing satisfaction.

Hyperovarism—Ovarian therapy is contraindicated in patients with ovarian irritability. So is thyroid therapy, save only in quite rare conditions where obvious hypothyroidism is superimposed upon a picture resulting from ovarian disease, and then it is given very cautiously.

The organotherapy of hyperovarism is identical with that suggested in menorrhagia, and, since here we have a condition of hypercrinism, the aim should be to overcome acidosis (100) and toxemia (99), and, by every means possible, to assist the detoxicating organs to do their duty (104), thus sparing the ovarian regulators from the irritation that inevitably comes from such toxemias. Pelvic depletion (106) is often helpful and, above all, there must be mental, physical, and sexual rest.

The reader's attention has been called to two antiovarian preparations—corpus luteum and mammary substance. These may be given by mouth alone or together, or injections of Endoluteum* may be combined with mammary extract, 10 gr. t.i.d. Menorrhagia, particularly menopausal menorrhagia, responds well to Mamma-Pituitary Co.,* which is of value in all forms of utero-ovarian congestion, hyperesthesia, and bogginess. This is a concentrate from mammary parenchyma with total pituitary substance plus a small dose of ergotin—enough to emphasize the essentially uterine influence of the associated endocrine products. The dose of this formula is one tablet at meals and at bedtime (q.i.d.). It is an advantage to double this amount for a week before and *during the flow*. It is then omitted for a week or ten days, to be resumed as before, and continued for several periods.

81. PARATHYROID DISEASE

Hypoparathyroidism—Tetany—Parkinson's Disease—Hyperparathyroidism

THE FOUR small organs hidden away behind the thyroid gland are more essential even than the thyroid itself, for the parathyroids are vital to life and control the detoxication of the acid and acid-like waste products through their regulation of the store of lime in the organism (16).

The parathyroid hormone has been called "a calcium mordant" and exerts a special destructive influence upon certain protein wastes, notably guanidine and similar substances. Since W. F. Koch, of Detroit, demonstrated this so effectively at the University of Michigan (*Jour. Biol. Chem.*, 1912, xii, p. 313; also *ibid.*, 1913, xv, p. 43), the causes of the hypoparathyroid states have been explained and we have learned the reason for the previous empirical use of parathyroid in Parkinson's disease, chorea, and other conditions of muscular hypertonicity.

HYPOPARATHYROIDISM is not so definite a clinical picture as hypothyroidism, and it is very much more rare, although both may be brought about by experimental surgical measures. Hypocalcemia is a common nutritional failing in certain disorders like tuberculosis and ulceration (94, 95), as well as in certain nutritional disorders involving the central nervous system. Since hypocalcemia can be modified quite uniformly by parathyroid therapy irrespective of the extent of the parathyroid damage, if any, empirical therapeutic interference with parathyroid as the agent is now an accepted measure no matter whether there is true parathyroid disease or not. For instance, hemophilia (60) is symptomatically benefited by parathyroid extract, but it is not known that this disease or other pathological variations in the coagulability of the blood are caused by parathyroid dysfunction. The same is true of chorea (46), in which parathyroid therapy is of symptomatic service in its treatment even though it is not proved that chorea is a direct result of dysparathyroidism.

TETANY—The complete removal of the parathyroid glands invariably results in tetany, an affection characterized by neuromuscular hyperexcitability manifested by tonic spasm of the muscles, local or general.

In adults it may occur following the administration of certain poisons, in connection with gastro-intestinal disorders (rare), and in the course of acute infectious diseases. The most common cause of tetany is loss of the parathyroids through disease or by their damage or excision in connection with thyroidectomy.

In children there is a form of nutritional toxemia known as spasmophilia (46), in which spasms occur in various groups of muscles, either spontaneously or on the slightest stimuli. This seems to be a form of tetany, and both cause and effect appear to be identical, differing only in degree.

Tetany must be differentiated from tics, myotonia, and habit spasms. The phenomena of tetany are quite typical, and several tests are available:

Erb's Sign—Increased electrical excitability of motor nerves using less than 5 ma. of galvanism.

Chvostek's Sign—Hyperexcitability of the facial nerve. Tapping in front of the ear produces a spasm of the muscles of the face.

Trousseau's Sign—Tetanic spasm of the hand and forearm following brief ligature of the upper arm.

Experimental parathyroidectomy gives the best evidence of the endocrine character of tetany, and it is confirmed by the success of replacement therapy with the parathyroid hormone. Hypocalcemia is the rule in tetany.

Treatment consists in the administration of lime and parathyroid extract—Paracalcin,* Parathormone, or Paroidin, from ½ to 2 cc. (from 10 to 40 units) intramuscularly one or more times daily, and Para-Spleen Co.,* from 1 to 3 sanitablets from two to four times a day. Calcium lactate, from 7½ to 15 gr. t.i.d. with much fresh milk, vitamin *D*, and sunlight treatment are excellent adjuvants. (The blood calcium should be determined at least every other day during active treatment, for the figure must not be allowed to go above 15 mg. per 100 cc.)

PARKINSON'S DISEASE—In this connection we may consider the shaking palsy usually called by the name of James Parkinson, of London, who described it in 1817, or by its Latin name, *paralysis agitans*.

Without a doubt, Parkinson's disease is a chronic progressive organic disease of the central nervous system, and possibly it is true that "there is no recognized specific cause." Paralysis agitans cannot be called an endocrine disease, for it has never been produced artificially by endocrine interference as have many other disorders of definite endocrine origin. We have seen that artificial hypoparathyroidism causes tetany but not paralysis agitans; also that parathyroid therapy can be used empirically to facilitate certain helpful changes in several other diseases besides paralysis agitans.

The endocrine aspects of paralysis agitans have been studied for some years, and it is conceded that the parathyroids are deserving of special consideration in this intractable disease. The picture of hypertonicity and muscular irritability is quite comparable in some respects to tetany, spasmophilia, and chorea, all of which are connected with hypoparathyroidism.

We are indebted to the late W. N. Berkeley, of New York, for his insistent emphasis of this matter ever since his first report (*New York Med. Jour.*, 1907, lxxxvi, p. 974). He gives three good reasons for the treatment of paralysis agitans with parathyroid:

"1. The blood calcium is often unusually low [just as it is in the hypoparathyroid states already mentioned]. Parathyroid raises this figure, thus increasing the calcium reserve. Lime, of course, is one of Nature's neutralizers.

"2. Certain protein-split products, such as guanidine, are often in excess in hypoparathyroidism. Parathyroid therapy lessens this excess, and at the same time gives symptomatic benefit. A condition sometimes called 'hyperguanidinemia' is not infrequently found in paralysis agitans, and it is known that these guanidine congeners have a special predilection for the nervous system.

"3. There are on record a number of autopsy reports of patients dying with paralysis agitans, showing parathyroid atrophy or pathology."

The best proof of the essential correctness of these conclusions about the connection between the parathyroids and Parkinson's disease is just this—the empirical use of parathyroid extract has been of symptomatic benefit in many cases of paralysis agitans. It cannot be cured—it is still "an incurable disease"—but it may be benefited. Speaking of the parathyroid therapy of paralysis agitans by mouth or hypodermic injections, Berkeley ("Principles and Practice of Endocrine Medicine," Philadelphia, Lea & Febiger, 1926, pp. 142, 147) says:

This treatment "has been productive of remarkable benefit in the majority of cases treated. This therapeutic test has been applied to hundreds of cases during a period of more than ten years past; the treatment has shown a steady and gratifying increase in popularity. The effect *may* be pharmacological, but it is worthy of note. . . . The effects of parathyroid in favorable cases are in every way beneficent. The rigidity and tremors are controlled, salivation is diminished, and restlessness and insomnia are relieved. Occasionally quite a miracle is worked."

There seems to be some difference between the paralysis agitans that follows encephalitis or serious infectious diseases with parkinsonism in comparatively young persons and in middle-aged patients. While parathyroid should be used in all cases, it is more likely to be beneficial in older persons.

So far as the prognosis from the use of parathyroid therapy in paralysis agitans is concerned it is difficult to make hard and fast statements. As Berkeley says (*loc. cit.*, p. 147):

"After good success with four or five patients in comfortable private life there usually come two or three which are failures—patients in whom even prolonged and excessive dosage with tablets and hypodermics has no effect. About 60 or 70 per cent. only of a large number of patients will be benefited.

Then there are patients who do excellently for a year or so, but later rapidly relapse. Physicians who have seen only two or three failures are pessimistic. Those who have had two or three brilliant successes are just as unjustifiably optimistic. The truth lies between."

Naturally, so chronic a condition as Parkinson's disease has to be treated at first in a routine way, and my recommendation is ½ cc. Paracalcin* (10 units) every day, plus Para-Spleen Co.,* 1 tablet at meals and at bedtime for the first month. During the second month, no injections are given, but the tablets are doubled in dosage. During the third month, another long series of injections, this time of 1 cc. (20 units) daily, is added to the oral therapy, which is continued at the previously increased dose. There is no record of any detrimental reaction following such dosage. Such treatment often has caused marked improvement in the facial mask, the tremor, the muscular incoordination, and the insomnia. Sometimes the insomnia and the indefinable internal nervousness are the first symptoms to respond.

Since January, 1931, a new idea has been introduced into the treatment of Parkinson's disease. My friend, T. Howard Plank, of San Francisco, having noted a series of cases of muscular toxemia that benefited from treatment with the new adrenal cortex hormone, tried a short series of injections of Adreno-Cortin* in a parkinsonian case. He writes:

"The more I use Adreno-Cortin, the more I am impressed with its value in various dysfunctions. My patient with Parkinson's disease continues to improve in every way; the pain is all gone, he sleeps well, appetite is good, and he can assist himself in every way. He is using his left arm, which has been helpless for more than two years, and can now raise it above his head. This patient is now using a Whitely exerciser, with his back to it to develop the arm and shoulder muscles and to bring the head erect. I consider this to be quite remarkable for less than three months."

During the last six months several hundred patients with Parkinson's disease have received Adreno-Cortin on the supposition that the excessive muscular activity (tremor, pill-rolling movements, etc.) causes a correspondingly increased muscular toxemia. These patients are always excessively fatigued and depleted. The cortical hormone may be spectacularly useful in many maximum degrees of asthenia, cachexia, and fatigue syndromes, both local, as in the heart and intestines, and general, as in Addison's disease (35). It facilitates the intramuscular chemistry, evidently by catalysis, hastening or completing the destruction of a larger amount of these fatigue poisons. Given at first solely on general principles, Adreno-Cortin has turned out to be of quite decided and prompt symptomatic benefit to many patients exhibiting the parkinsonian syndrome, but it is not invariably helpful, nor does it interfere with parathyroid therapy.

One cannot believe that this influence reaches the source of the difficulty, nor that it changes the reality of the previously accepted endocrine fundamentals (regarding the parathyroid influences); but, as has been noted in cancer (44), Addison's disease (35), and other hopeless conditions, even the symptomatic benefit from a course of Adreno-Cortin* is encouraging.

HYPERPARATHYROIDISM—For years after the clinical states associated with hypoparathyroidism were determined, this condition was but a technical clinical entity, theoretically possible but unknown.

During the last five or six years, however, there has been some interest aroused in the possible connection between tumors of the parathyroids and bone diseases. As far back as 1906, J. Erdheim, of Frankfurt (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1906, xvi, p. 632), connected von Recklinghausen's disease (osteitis fibrosa) with the parathyroids. The subject was not considered of interest until 1925, when S. Hoffheinz, of Leipzig (*Virchow's Arch. f. path. Anat. u. Physiol.*, June, 1925, cclvi, p. 705), reported on forty-five cases of parathyroid hyperplasia or neoplasm. Twenty-seven of these patients had bone disease, seventeen being classified as osteitis fibrosa, eight as osteomalacia, and two as rachitis.

Basing one's expectations on the information about hypoparathyroidism, the clinical findings are as would be anticipated. Several reports indicate that these cases show such opposites as (1) a great increase in the excretion of lime, (2) serum-calcium increases of from 13 to 23 mg. per 100 cc., (3) fairly constant and marked muscular hypotonicity—all antitheses to the findings in parathyroid tetany.

The bone findings are pain, greatly diminished density of the bone shadows as shown by the radiograph, and occasional spontaneous fractures. Certain traumatic bone cysts and osteodystrophia fibrosa are in the same category with the foregoing. It is believed that the trauma is a local inciting factor, the underlying cause being the constitutional defect arising from the dyscrinism.

Prospects for treatment are not so good in hyperparathyroidism as in hypoparathyroidism (unfortunately this is uniformly true in other endocrine irregularities). Where the serum calcium is high, the calcium balance negative, and there is a tendency to hypotonicity and hypoexcitability of the neuromuscular system as well as pronounced rarefaction of the bones, the treatment is limited to surgery—parathyroidectomy. Perhaps some day we may find a balancing antiparathyroid hormone comparable with several other endocrine chalones. If some of the experimental findings mentioned in the literature can be relied upon, we may look for this balancer in the adrenal cortex.

82. PELLAGRA

THE ESSENTIALLY nutritional character of pellagra has caused several Southern endocrinologists to express the hope that a solution of the problem may be found in the endocrines.

All of the few cases of pellagra that I have seen have been so far advanced that nothing could be done for them. It was evident that these patients were sadly depleted.

The anemia of pellagra usually responds well to liver therapy, and Heparnucleate* has been found a helpful addition to the symptomatic treatment. It is possible that the benefit from such treatment is not due to the hemopoiesis alone. An Indian investigator, B. C. Guha, of Calcutta (*Lancet,* April 18, 1931, ccxx, p. 864), working in the University of Cambridge, recently found that the liver extracts in general use in the treatment of anemia are unusually potent sources of vitamin B_2 and comparatively poor in vitamin B_1. Hence, it appears

". . . that the commercial liver extract, besides being a rich source of the pernicious anemia factor, is extremely rich in the pellagra-curative factor. It should, presumably, provide a better material than yeast for the cure of human pellagra."

An interesting point regarding the frequency of pellagra has to do with the bread-eating habits of those who live in parts of this country where pellagra is common. Yeast bread is practically never eaten, and, since it has been shown that the heat of baking is not sufficient to destroy completely the pellagra-preventing vitamin, it would seem that it might be a public health measure of wide-spread value to change the kind of bread these people eat.

As a result of some research work carried out in the laboratories of the United States Public Health Service, J. Goldberger and W. H. Sebrell (*Pub. Health Rep.,* Dec. 12, 1930, xlv, p. 3064) emphasize the fact that liver therapy has broader potentialities in pellagra than in anemia. These writers state:

"It appears that Minot's liver extract, given to dogs on a basic black-tongue-producing diet, in a daily dose equivalent to 100 Gm. of fresh liver, has a very definite delaying effect on the occurrence of symptoms, and when fed to dogs in an attack of black tongue has a very definite curative effect. The most reasonable explanation for this action seems to be that the liver extract carries the antipellagric vitamin with it. In view of the evidence herein presented, it seems that Minot's liver extract is a fairly good source of the antipellagric vitamin, and given in larger quantity would be of value as a temporary expedient in the treatment of pellagra."

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83. PITUITARY DISEASE

Acromegaly—Gigantism—Anterior Hypopituitarism—"Pituitary Goitre" —Posterior Hypopituitarism—Pituitary Dwarfism—Pituitary Tumor.

ONE OF the vital initiators of function in the body is the pituitary gland, or hypophysis. We have seen that it purveys to the body nearly a dozen vital chemical messengers (18) that play essential rôles in the growth of the bones, the development of the sex mechanism, and the regulation of nutrition, to mention only three of the major services rendered by this gland.

Because certain diseases of this organ cause clear-cut syndromes, such as acromegaly and gigantism on the one hand, and asexualism and obesity on the other, the tendency has developed to think of the pituitary gland in terms of maximum dyspituitarism. This tendency has been confirmed by the discovery that fierce headache, epileptoid seizures, and even blindness, may be caused by pituitary neoplasms whose treatment is radical and usually unsuccessful.

Of course, the ultimate dysfunctions of the pituitary, with their structural changes and spectacular symptoms, are important realities; but, compared with functional endocrine disorders, they are extremely rare. To most clinicians to-day this will seem fairly obvious but it was not always so. As recently as 1925, so famous an internist as Joseph L. Miller, of Chicago, publicly doubted in these words the actuality of the fairly common pituitary headache ("Glandular Therapy," Chicago, American Medical Association, 1925, p. 61):

"There has developed recently considerable literature on the value of pituitary substance by mouth in the treatment of 'pituitary headache.' A review of the literature fails to reveal a headache that justifies this name, except in cases in which a tumor is present. In many reported cases the headache is definitely migrainous in character. . . ."

Measured by the frequency of their occurrence, and by their therapeutic hopefulness, the less ostentatious dyspituitarisms are of first importance. Further to emphasize this rather depreciated truth, I shall consider pituitary diseases in two main groups—the major (rare) and the every-day cases.

ACROMEGALY is a dystrophy characterized by overgrowth of the body, especially the long bones, due to increased activity of the anterior lobe of the pituitary gland. As the name indicates (*akros*—extremity; *megale*—great) the condition is most marked in the extremities, although there is also facial enlargement. The skeletal abnormalities are probably caused by changes in the rate of ossification in the epiphyses.

It was in 1886 that Pierre Marie, of Paris, published a clinical description of the disease, and called it "acromegaly" (*Rev. de méd.*, vi, p. 297). By the classical description of these patients, he laid the foundation for all subsequent study of the subject, although he made no attempt at the time to point out the etiology. However, Fritsche and Klebs ("Beitrag zur Pathologie des Riesenwuchses," Leipzig, 1884) seem to have been the first to suspect the possible relation between acromegaly and the ductless glands, for at autopsy they found enlargement of both the thymus and the pituitary.

Minkowski argued that, since myxedema is related to changes in the thyroid, and is accompanied by trophic changes in the skin and extremities, acromegaly must be related to disturbances of the hypophysis, for this disease, too, is evidenced by trophic disturbances.

By this weak link, the pituitary gland and acromegaly seem first to have been joined together. The early workers did not guess the exact nature of the disturbance, and for years there were grave doubts about the very possibility of pituitary involvement.

Hyperpituitarism before adolescence is manifest most definitely in gigantism, whereas after the bones have finished their normal growth, the changes are not so much in their length as in their size. There is a gradual enlargement of the hands, feet, jaws, and chest, and quite commonly a dorsal cervical kyphosis.

Many cases of acromegaly occur without actual enlargement of the pituitary (aneoplastic type), although it is not infrequent to find a considerable increase in the size of the gland with erosion of both the anterior and posterior clinoid processes and other gradual manifestations of pituitary tumor (*q.v.*).

Since acromegaly is a nutritional disease, by the time the osseous changes are evident, changes have taken place also in the vegetative nervous system, the metabolism, and the other endocrine glands besides the pituitary.

As the endocrine upset increases in importance and involves the associated glands, there are added to the bony changes modifications in the skin somewhat similar to myxedema; the nose is thickened, and the lips are enlarged. Of course, the already massive jaw is accentuated by the thickness of its covering. The buccal mucosa is thickened, and the tongue greatly enlarged.

The evidences of associated dyscrinism are manifested chiefly in the thyroid (skin dry and puffy) and in the gonads (amenorrhea and impotence).

Glycosuria is quite usual. The marked fatigue, so common in these cases, is probably of adrenal origin. There are liable to be headaches and other symptoms of intracranial pressure such as one expects in pituitary tumors.

J. Caussimon, of Bordeaux (*Jour. de méd de Bordeaux,* Sept. 10, 1920, xci, p. 462), reports a case of acromegaly in a woman, age 36, associated with signs of pluriglandular insufficiency, *viz.,* symptoms attributable to the thymus, thyroid, and ovary. Strangely, the X-ray showed no enlargement or deformity of the sella turcica. Out of thirty-three cases of acromegaly that Caussimon collected from the literature between 1886 and 1919, no mention is made of persistent thymus in twenty-seven, the presence of characteristic retrosternal dullness is noted in four, and a persistent thymus was found in two. In this series the thyroid was sometimes atrophied and sometimes enlarged. Occasionally there was exophthalmos. In his own case there was definite thyroid atrophy, and the development of the subcutaneous tissue, appearance and texture of the skin, and scantiness of hair resembled myxedema. Disturbance of the ovarian function was shown by amenorrhea, which had been present from the onset, in thirty of the thirty-three cases.

There is no dependable treatment of acromegaly because, by the time the diagnosis is made, too much damage has been done. Then, too, it is the general rule that hyperendocrine conditions do not respond to endocrine therapy so satisfactorily as their antitheses. However, it is not infrequent to find a patient manifesting all the anatomical signs of acromegaly, who really has hypopituitarism plus hypothyroidism. In these cases, thyro-pituitary therapy will help to replace some of the missing hormone stimuli. But the acromegaly itself cannot be expected to respond to treatment. Pituitary substance often seems to produce headache, thus incidentally confirming the reality of its potency when given by mouth.

Usually, the treatment of acromegaly is not encouraging and the prognosis is poor, though it varies with the type of pituitary involvement. The treatment of these cases really resolves itself into an attempt to modify the associated dyscrinism.

GIGANTISM—There is probably no real difference between gigantism, acromegaly, and hyperpituitarism. From a therapeutic point of view, gigantism is one of the most difficult of the endocrinopathies. Ordinarily no endocrine abnormality is suspected until it is noticed that the bones are unusually long and perhaps the face appears a little more bold. There soon develops a headache, which is later connected with pituitary enlargement. The patient is usually in an irretrievable state before the diagnosis is made.

The treatment of gigantism is symptomatic. If the patient is suffering as a result of a change in the functional capacity of other glands, the indicated endocrines are in order. The most common therapy in these cases is directed at the usual hypogonadism (58) and pituitary insufficiency.

The information developed in the study of acromegaly and gigantism and their antitheses—acromicria and dwarfism—has led us to many improvements in the treatment of the latter. Too much emphasis cannot be laid on the fact that hypo-endocrinism lends itself very decidedly to suitable organotherapy, whereas hyperendocrine conditions usually do not respond nearly so well.

ANTERIOR HYPOPITUITARISM—To the trained observer, the signs of pituitary insufficiency are clear enough and the diagnosis is comparatively easy. (See Section III, Chapters 26, 27, and 29.) But most of these manifestations are appreciated too late to accomplish very much in a therapeutic way.

Major hypopituitarism, if such a term may be used, does not offer much hope of benefit. It does respond to the indicated treatment, but not in the degree that we expect thyroid or adrenal dysfunctions to react to the corresponding therapy. The Lorain-Levi type of dwarfism does not respond well, nor does the adiposogenital dystrophy of Fröhlich. The reason is clear—these dystrophies are associated with irrevocable pituitary damage and anatomical changes in the sellar cup (wherein the pituitary lies), which mechanically interfere with the possibility of hypertrophy of sound tissue through the principle of homostimulation (Hallion's law, see page 56).

Referring to a type of patient whom he describes as suffering from "a new pluriglandular compensatory syndrome," Walter Timme, of New York (*Endocrinology,* July-Sept., 1918, ii, p. 218), says:

"In our judgment, it is the pituitary gland which is here the critical factor. . . . If the pituitary possibly could become hyperplastic and hyperactive . . . compensation might be accomplished. Such tendency to hyperplasia in a small cavity would, of necessity through pressure, produce headache. . . . Curiously enough, in all our cases, the feeding of pituitary gland in fairly large quantity disposed of many, and at times of all, of these symptoms."

On the contrary, Engelbach believes that "the simple oral administration [of pituitary] has not been found efficacious except in mild adult hypoactivity or in the initial insufficiencies of childhood." He expresses preference for the hypodermic products, recommending from 1 to 2 cc. of Antuitrin daily or less frequently, depending upon the severity of the symptoms and the patient's reaction to the treatment. However, referring to the active principle of the lobe or lobes involved, he also says, "This substance is given both hypodermically and orally at the same time."

Fortunately there are many cases with hypopituitarism in which other factors are prominent and for which the indicated pluriglandular therapy

gives fair satisfaction. This presumably is why Harvey Cushing, of Boston (*Jour. Am. Med. Assn.,* June 18, 1921, lxxvi, p. 1721), said:

"A great number of these patients have been induced subsequently to follow out prolonged courses of glandular treatment. I cannot say that I have ever seen any definitely beneficial results of so doing except when there has been some concomitant thyroid want indicating the coincidental use of thyroid extract."

Without a doubt, then, pluriglandular therapy of a hypocrine syndrome in which there is a functional pituitary factor offers us the most clinical satisfaction. Which of these syndromes may be treated with good prospects of results? There are several, each of which is a subject by itself which needs consideration and treatment from a much wider point of view than the pituitary alone. There are: Mongolism (46), infantilism (83), obesity (79), and pituitary headache (59).

I have never treated a case of hypopituitarism with pituitary therapy alone, and I am frank to say that the failures of some of my colleagues have been turned into successes by the needful pluriglandular therapy.

"PITUITARY GOITRE"—For some time I have said that a condition could develop in the pituitary analogous to simple goitre. I have called this "pituitary goitre." The idea was, by a descriptive name, to indicate a parallel in the causes of many thyroid and pituitary enlargements. Both glands may increase in size because of inherent shortcomings or in response to increased physiological demands. Recently I discovered that J. P. Simonds, of Chicago ("Endocrinology and Metabolism," Vol. I, p. 795), refers to a condition called *struma pituitaria,* which is:

". . . a uniform enlargement of the entire anterior lobe of the hypophysis due to multiplication of its cells. . . . It is a question whether this is true tumor any more than a struma of the thyroid is a tumor of that gland. It seems more likely that a struma is a hyperplastic, rather than a neoplastic, condition—a sort of superhyperplasia."

The syndrome is that of a moderate hypopituitarism coupled with the findings of pituitary neoplasm (30). But it differs from the real pituitary tumor in its prompt response to organotherapy, exactly as simple goitre differs from thyroid adenoma (57).

A case in point is heartening evidence of the possibilities of endocrine therapy: A school boy, aged eleven, was brought for consideration because he was "hard to manage." He was a serious problem at home because of sleeplessness, irritability, nervousness, thoughtlessness, destructiveness, and inability to stick at anything from study to eating! Epileptoid attacks had led to the administration of luminal, but without improvement. He had a right-

sided external strabismus, and his brother two years younger had overtaken him in both growth and school work.

Within a month after the initiation of Antero-Pituitary Co.,* the whole picture was changed—the boy slept well, behaved well, sat still when necessary, and the squint seemed to be improved. After another month he was gaining in his studies, and the nervousness was all gone. Three months later he had gained an inch in height. Although apparently well, he is still under treatment, for he is still an endocrinopath, and six months is a short time for the treatment of such a case.

POSTERIOR HYPOPITUITARISM—In posterior lobe insufficiencies with the two chief manifestations—polyuria (51) and obesity (79)—treatment may be carried out with posterior lobe products such as pituitrin, infundin, liquor pituitarii, etc. In his contribution to Cecil's "Text-Book of Medicine" (Philadelphia, W. B. Saunders Co., 1930, p. 1185), William Engelbach calls attention to the three clinical reactions following such injections, which enable us to determine the physiological dose: (1) The *vascular* reaction, occurring a few minutes after the injection of a comparatively small amount, consists of marked pallor lasting about fifteen minutes. (2) The *intestinal* reaction follows larger doses and consists of abdominal cramps followed, about twenty minutes after the injection, by defecation, which is due to the contraction of the alimentary muscles. Engelbach considers this an index of maximum toleration which should not be exceeded. In ordinary circumstances the dose is 5 min. of pituitrin (surgical—containing 20 international units per cc.), increased by 1 min. from time to time until this intestinal reaction occurs. Because of this reaction, the only way to increase the dosage of pituitrin is to decrease the intervals between the injections. When still larger amounts are given, there is (3) a *general* reaction, which causes marked pallor lasting many hours, palpitation, and tachycardia, and perhaps syncope. From this it will be clear that the treatment of posterior hypopituitarism should be attempted only under the most careful control.

PITUITARY DWARFISM—The subject of dwarfism already has been discussed under "Childhood Endocrinopathies" (46), but some comments will be in order here regarding the so-called "hypophyseal dwarfism." True pituitary dwarfism is not common, for practically every notable growth defect is of pluriglandular origin.

Pituitary dwarfs show no great abnormality in the proportion of the body structures, nor does the ratio of the length of the trunk to the length of the

extremities show any striking anomalies (30), but the feet and hands are often quite large compared with the length of the body. X-ray studies frequently show delayed epiphyseal ossification.

The sella turcica is practically always abnormal, and pituitary tumors often develop later in life. Gordon Holmes, of London (*Brit. Med. Jour.*, Dec. 4, 1926, ii, p. 1035), says that in the third decade of life pituitary dwarfs usually become prematurely senile; they lose weight and their skin becomes thin, dry, and wrinkled; they may grow either bald or gray.

There is a difference between pituitary dwarfism and infantilism; and the latter is much more commonly seen. Here the stature is often, though not invariably, dwarfed, and the general development is slender. In both conditions there may be a childlike configuration. Infantilism is differentiated by non-development of the secondary sex characteristics, hypoplasia of the genitalia, mental retardation, and the persistence of childhood attributes into adult life.

The treatment of growth dystrophies involving the pituitary should include aggressive pituitary feeding. For years I have treated these cases with the same pluriglandular formula prepared for the treatment of developmentally defective children (46). The results have been growth increases of from 3 to 6½ inches in a year, this last figure being in a youth who had not grown for four years. It is not uncommon for the stature of a young man in his late teens, or even older, who has not grown for years, to be increased as much as six inches.

There is a concentrate from the anterior lobe of the pituitary, peculiarly rich in the growth hormone, which is known as Accretin* (18). The dose is indeterminate. The minimum amount is four 5-gr. capsules a day, and as much as three capsules four times a day have been taken without detriment.

It is clear that if hypogonadism or obesity is associated with the dwarfism, the treatment should take this into consideration (58, 83).

PITUITARY TUMOR—In the diagnostic information given in Chapter 27, attention is directed to the variations in the symptoms of dyspituitarism, which depend upon the time of its development and the length of its duration. The symptoms of pituitary tumor depend also upon these time factors and, of course, upon the type of pituitary pathology and the cerebral and sellar elbow-room.

Naturally a pituitary neoplasm is virtually never diagnosed early. This difficulty, coupled with the structural changes, makes treatment very unsatisfactory. Fortunately new growths of the pituitary are rare, representing, according to Engelbach, less than 4 per cent. of the cases of definite dys-

pituitarism, which, of course, are only a comparatively small proportion of the cases in which there is a pituitary dysfunction.

The treatment of pituitary neoplasms is divided into four parts: (1) control of the dyshormonism connected with the hyperfunction or hypofunction; (2) treatment of the headache and other results of the intracranial pressure; (3) attempts to change the hyperplasia by recourse to X-ray or radium; and (4) surgery.

Pituitary dysfunction produced by a neoplasm is treated exactly as are the aneoplastic types already referred to. It is possible, in certain cases, to reduce the enlargement by regulating a related endocrine upset. Though this is not often feasible, it is not unreasonable, considering some of the clinical responses that follow the treatment of goitre. In the so-called "pituitary goitre" or simple enlargement, such hyperplasia is supposed to be more intercellular than intracellular, and more of a colloid nature than a true hyperplasia of the glandular tissues. Where there is also marked hypothyroidism, it may be possible that there is some cellular infiltration of the pituitary itself just as has been shown to be so common elsewhere (67).

Pituitary headache associated with tumors is not easily controlled. Because suitable pituitary feeding so often benefits the functional types (59), its failure to give relief suggests an organic difficulty. Thus it becomes a diagnostic measure.

Radium is not so effective as the X-ray because it is difficult to secure satisfactory penetration, and it is possible to focus the X-ray. The dosage varies, but in general it should be higher and longer than for treatment of superficial lesions. Push the dosage, but only under the most accurate control. Some advise the X-ray only as a supplementary measure, but it is the best single hope in the treatment of a pituitary growth that has not responded to other reasonable therapy.

Surgery is the ultimate recourse in treatment of tumors of the hypophysis. It is a serious, major procedure with a high mortality and only fair prospects should the patient survive. X-ray exposure is recommended after surgery because pituitary tumors may recur.

The type of neoplasm most responsive to treatment is the pituitary gumma, which may disappear as if by magic under intensive antisyphilitic treatment. Organotherapy is directed more at the general endocrine dysfunction than at the pituitary itself.

84. PREGNANCY

Preventing Transmissible Defects—Anemia during Pregnancy—Hypothyroidism—Goitre in Pregnancy—Prophylactic Iodine Therapy—Toxemias of Early Pregnancy—Emesis Due to Protein Sensitization—A Placental Protein Test—Producing an Artificial Immunity—A Routine Therapy—Luteal Hormone Imbalance—Headache during Pregnancy—Toxemias of Late Pregnancy—Hepatic Causes of Eclampsia—Clinical Success with Liver Extracts—Mammary Toxemia in Eclampsia—Delayed Labor—Dystocia Due to Infiltration.

THE FORTUITOUS nutritional changes that occur so commonly in pregnancy are results of endocrine cooperation. Many of the developments of gestation—from the nesting of the newly impregnated ovum to the expulsion of the fetus—are brought about by hormone intervention.

PREVENTING TRANSMISSIBLE DEFECTS—The endocrines are doubly vital during pregnancy, because they are making their impress on the growing fetus, especially on its budding glandular system. It is particularly important, therefore, to consider the endocrines in the pregnant woman, not only for her sake, but in a prophylactic way for the sake of her unborn child. Untreated dyscrinism during gestation undoubtedly is responsible for what Timme calls "the endocrinopathic inheritance" (46).

ANEMIA DURING PREGNANCY—Some women grow fat and robust during pregnancy; others are toxic, ill, and anemic. The latter should be given special attention in every way possible. The early control of the anemia of pregnancy is a means of avoiding more serious trouble during the later months, if only for the fundamental reason that "the blood is the life," and poor blood predisposes to poor nutrition, improper detoxication, and insufficient endocrine activity. It is a good rule never to allow the red cell count to fall below 4,000,000 during pregnancy; and there is no harm in bringing it up to 5,000,000, which is a high normal for women.

Hemopoiesis, which is easily accomplished by liver therapy, is of double value at this period. Though it is impossible to say what might have happened in a given case had it not been instituted, it is certain that liver therapy with the hemopoietin-ferric-nucleate product, Heparnucleate* (13), is beneficial in the anemias of pregnancy. The dosage depends upon the circumstances and is regulated by the red blood count, but the contents of one tube twice a day at meals for a week, then once daily for a week or longer, is the usual procedure. The treatment is prolonged or resumed as necessary.

So far there is no record of a patient's having a postpartum infection after having taken this treatment, but undoubtedly this is attributable to the circumstances more than to the patient's resistance. It is a fact, however, that the nucleins are leukocytogenetic, and materially increase resistance as well as nutrition.

HYPOTHYROIDISM—Many women exhibit a latent thyroid defect when the stress of pregnancy begins to take effect. This is particularly true in two types: (1) those who have had thyroid trouble during puberty (57), and (2) those who for a long time have had ovarian imbalance such as amenorrhea, dysmenorrhea, asexualism, etc. In these cases one usually uncovers a clear-cut history of a thyroid heredity—in mother, aunts, grandmothers, or even sisters—and the anamnesis reveals either previous thyroid manifestations or the kind of background that one expects in hypothyroidism, *e.g.*, prolonged toxemias, serious infections or infectious diseases, malnutrition or obesity, and a slowed metabolism.

The state of pregnancy puts added demands on the thyroid gland. If it is presumably normal, the thyroid has plenty of resilience to care for these demands; if it is defective, it inevitably will fail. Unfortunately, the results of some of these shortcomings are not seen until they manifest themselves in the child.

The immediate findings in hypothyroidism in pregnancy are (1) goitre, (2) headache, (3) constipation, (4) "achiness" that sometimes is mistaken for rheumatism, (5) dermatoses involving the nutrition of the skin and its appendages (dry skin, brittle hair, cracking nails, etc.). Sometimes there are no noticeable symptoms, but the patient does not do well, and the basal metabolism test is found to be low. Goitre is first sought for, and thyroid extract is given as a diagnostic measure as much as for the actual benefit that it may produce. Where hypothyroidism is at the base of the difficulty, such organotherapy is amazingly helpful, not only to the mother but also to the infant. It is now generally conceded that endocrine abnormalities in children are built upon a foundation of maternal endocrine defects during their gestation. Further, a baby weighing 10 or more pounds almost invariably is a potential endocrinopath, and too often this is the first indication of the mother's own endocrine upset. An oversized baby is an abnormality, and, had steps been taken to overcome it, there would have been more comfort to the mother, less dystocia, and a far better chance for the child.

Hypothyroidism during pregnancy is one of the endocrine disorders that respond most pleasingly to treatment. A little thyroid or iodine, or both, greatly benefit mother and child.

GOITRE IN PREGNANCY—There are two outstanding reasons for the enlargement of the thyroid during pregnancy: toxic stress and inherent susceptibility. Naturally the stress arouses the hypertrophic reaction more easily if the thyroid is already suffering from the limitations placed upon it by heredity, previous strain, and geographic location.

A simple thyroid enlargement during pregnancy is usually of no serious import. Some authors consider it to be normal. They not only regard the hypertrophy as physiologic, but suggest that pregnant women in whom there is no such thyroid response are more liable to have albuminuria. This is explained by the fact that the increased service of the thyroid is necessary in the detoxication of certain poisons that accompany pregnancy, and, without this, the toxemia becomes so great that it may cause renal injury.

There is a great difference, however, between a physiologic swelling of the thyroid and a real goitre. The latter may be considered as a warning that pregnancy is putting an undue strain upon the thyroid, and then active steps should be taken to prevent the reactions on the part of the other endocrines—including those of the unborn child. Fortunately, this may be accomplished by the use of iodine, a procedure so simple that it should be a standard routine.

Thyroid hypertrophy with signs of sympathetic irritability is quite another matter—it may be a real danger sign, and the beginning of the road that leads to true Graves' disease.

The basal metabolic rate does not differentiate between these two types of goitre so accurately during pregnancy as under other circumstances, for gestation, like physical activity and fever, interferes with a proper measurement. The clinical symptoms are the best guide, and the result of thyroid therapy is the best confirmation. It is better to plan this rather than to prescribe treatment that does not turn out so well. My Thyroid Function Test (31) is a routine, planned-in-advance measure. Not only does it enable one to differentiate between thyroid apathy and thyroid sensitiveness, but in the most usual type of case—the simple goitre with hypothyroidism—it may result in much clinical improvement, which is marked down on the patient's opinion-record of the doctor's skill. In fact, I have seen simple goitres disappear completely during the administration of this test, the reason being that the amount of thyroid given was enough to obviate the need for the thyroid to enlarge in order to meet its added obligations.

The treatment of goitre during pregnancy is virtually that of hypothyroidism or hyperthyroidism, as may be the case. It is a good policy to advise measures calculated to lessen toxic stress. These are good elimination, alkalinization (remineralization), and rest.

PROPHYLACTIC IODINE THERAPY—With very few exceptions, every pregnant woman benefits from iodine. As little as only one average dose a week may suffice. Of course, where there is more marked hypothyroidism, with other symptoms besides the goitre, larger doses must be given. Thyroid therapy is a good adjuvant.

Such prophylactic therapy is particularly appropriate in women in whose families there is a tendency to goitre, and in those localities where goitre is endemic, as in the southern and western cantons of Switzerland, the county of Derbyshire, England, and the Pacific Northwest or the Lake Region in the United States. (See Chapters 57 and 103.)

TOXEMIAS OF EARLY PREGNANCY—In 1916, while I was working with various placental extracts, it happened that my attention was called to several women in early pregnancy who were suffering from anaphylaxis. My thought sequence was something like this: As hypersensitive women are defective in some subtle way that makes them more susceptible to certain proteins, why might not this susceptibility make them react to placental proteins just as they do to other proteins? Since allergy shows itself not only on the skin, but on the mucous membranes (asthma, due to bronchial irritations, and colitis, due to certain toxins), why might not the principal location of the anaphylactic manifestations in pregnant women be in the alimentary mucosa—the stomach in particular?

My immediate reaction was: Try it and see. I had no laboratory in which to experiment, and, even if I had had, this problem was unsuited to animal experimentation. But I did have a placental extract containing the presumed offending protein or something closely akin to it, and patients whose extremity made them more than willing to try anything. The clinical test was made, and the desensitization appeared to be a success; it was repeated again and again. For more than fifteen years, it has been helpful in the majority of cases treated.

EMESIS DUE TO PROTEIN SENSITIZATION—The discomforts of early pregnancy, which too often develop from simple nausea into occasional vomiting and still later into hyperemesis gravidarum, are now believed to be a manifestation of protein sensitization. One or more new structures are delivering into the blood, with which they are so generously nourished, certain cellular wastes that are equally new to the rest of the body. As many women quickly accommodate themselves to these protein products, the discomfort that they are believed to cause is short-lived. Others, however, seem unable to accustom themselves to these substances, and, like those who are

sensitive to other proteins such as strawberries, shell-fish, eggs, etc., or to air-borne proteins that produce hay-fever, they react in varying degrees to the influence of these subtile substances.

The fact that this form of placental toxemia commonly is limited in degree, and especially in time, lends reasonableness to the probability that the body ordinarily accustoms itself to these foreign substances and in due time they are allowed to circulate in quantities that previously would have been dangerous. In other words, the body normally carries out its own desensitization.

A PLACENTAL PROTEIN TEST—In 1926 it occurred to me that this notion might be made more acceptable, so a concentrate of placental protein was prepared and made available in capillary tubes. This Placental Protein Test was made in many women who were suffering from hyperemesis, which, it was presumed, was a form of placental anaphylaxis.

Quoting from my announcement of this new test in *Clinical Medicine and Surgery* (April, 1927, xxxiv, p. 279):

"A series of dilutions of placental proteins has been prepared for use in a skin test which in every way corresponds to the many tests with different proteins now available for this purpose. The procedure is identical with these, and the deductions are comparable.

"The method suggested is as follows: Wash an area on the upper arm (or elsewhere, as desired); paint with tincture of iodine; wash off the iodine with alcohol; allow it to dry; then, with a scarifier similar to that used in vaccination (or with a sterile needle) make four slight scarifications from one to two inches apart. Upon each of these denuded areas, deposit one drop from each of the capillary tubes supplied, which represent three strengths of the dilution, A, B, and C, while D is sterile water for the control. Allow the drops to dry thoroughly. Protect with a piece of sterile gauze.

"These vaccinations should be inspected at twenty-four-hour intervals and a note made of their appearance. The clinical deductions in regard to the reactions of various patients are made upon exactly the same basis as are those with other protein sensitization tests. The final diagnostic conclusions have yet to be made, but logically they should be most interesting, and they may be helpful in elucidating still further this particular phase of a subject regarding which everything is not yet known."

The foregoing test enables us to determine the sensitivity of a patient to the placental protein and to measure it roughly. If the test is positive, this sensitiveness is a factor to be considered, and we have a reason to proceed with the attempt at therapeutic desensitization by procedures somewhat similar to those in general use in the treatment of other forms of allergy, etc.

PRODUCING AN ARTIFICIAL IMMUNITY—Granted, for the moment, that this theory has a reasonable basis, why should it not be possible to bring about an artificial immunity to such present or prospective placental protein intoxication? And why might this not be accomplished in the same way that other forms of protein sensitization are controlled, *i.e.*, by administering the same proteins in gradually increasing amounts, thus bringing about an artificially increased tolerance to the offending substances?

Originally this was made a basis for clinical trial in a few patients, who, confronted with an "inevitable" abortion, were willing to postpone surgery long enough to try one more measure. A fresh human placenta was shredded, the greater part of the peculiar connective tissue whorls combed out, and the pulp desiccated in vacuo, and put up in gelatine capsules. An arbitrary dose was given, which was repeated and increased. The patient knew nothing of the character of the treatment; she swallowed it, and fought hard to keep it down. Usually retention was aided by judiciously arranging the doses to alternate with "free periods" (of rest and sleep), occasionally by the simultaneous use of sedatives, and often it was given in an enema.

The results were astonishing. Several of the patients were admittedly in extremis and the new treatment was tolerated by the medical attendants who could not well deny the importunities of the relatives. Not every case responded in the same degree or manner, for some acted quicker and more thoroughly than others. Occasionally the woman's troubles seemed to be aggravated, and the treatment failed. This emphasizes the distinctly non-drug character of the remedy and also the fact (since tested by many observers) that the reactivity to the administration of this placental extract evidently depends largely upon the responsiveness of the patient, which always is an unknown quantity to begin with.

Several really critical cases were cured entirely. Within a week or ten days—occasionally in as short a time as three or four days—the patient was better. The vomiting was relieved both in degree and frequency, and later subsided into a nausea or near-vomiting, which was overcome in a short time. Occasionally a patient would appear to be over her difficulty but it would recur. In such cases, a renewal of the treatment invariably brought control, which was made permanent by prolonging the organotherapy. This seems additional evidence against the inevitable suggestion of coincidental benefit.

Let us repeat that all the first cases thus treated were severe ones. As with other advanced forms of organotherapy in new hands, the opportunity was not given in early or simple cases. Those who permitted its use often did so grudgingly and even scoffingly. Perhaps it was a colleague who had brought

the attending physician's attention to this method, and, as I have been informed, the treatment was usually accepted with doubt and forebodings.

The development of the remedy and its gradual acceptance by the profession have made possible a better proportion of good results, for it is employed at a very much earlier and less complicated stage of the difficulty. Even now, we occasionally meet a flat failure, which, however, is more than offset by the scores of really spectacular results. In our series, two-thirds of the cases thus treated were distinctly benefited, and the difficulty was controlled in varying periods.

So far as I am aware, the basis of this method was original with me. At least, I was the first to make it clinically possible in the United States and Great Britain. Since that time several interesting, confirmatory items have appeared in the literature. In his book, "The Endocrines" (Philadelphia, W. B. Saunders Co., 1920, p. 319), S. W. Bandler, of New York, agrees with me in this theory. He says:

"This nausea and vomiting represent a reaction on the part of the system to the introduction of the placental secretion. If a stable adjustment results quickly, the nausea disappears quickly. In this readjustment, undoubtedly (in the cases which vomit decidedly), we are concerned with a toxic influence produced by the placental extract or with an exaggerated reaction on the part of the posterior lobe, with resulting hypersensitiveness of the gastro-intestinal tract."

Eugene Cary, of Chicago (*Med. Standard,* Feb., 1918, xli, p. 55), reports having used this method with splendid results. He says:

"I have collected thirteen cases of vomiting of pregnancy, which have occurred at different periods during gestation. One or two of these, developing later in pregnancy as they did, might have developed into the pernicious type had they been allowed to continue. Of these thirteen cases, two were lost sight of. Of the remainder, seven ceased vomiting within a day or two and the nausea soon disappeared. Two improved and remained fairly free from nausea, although the administration of the extract had to be continued over a longer period of time. In the remaining two cases, the results were not satisfactory; one was neurotic."

An interesting observation made by A. Y. P. Garnett, of Washington, D. C., appeared in the *American Journal of Obstetrics* (Aug., 1917, lxxvi, p. 303). He reasoned that hyperemesis is a toxemia, but, instead of establishing an artificial immunity, he attempted to give the patient an immunity already prepared in the body of another. Accordingly, two patients were given a blood transfusion from donors who had just been delivered. Improvement was rapid in both cases, but one required a second transfusion; however, the results were none the less gratifying.

A ROUTINE THERAPY—To revert to the fundamentals of this method: The idea is to have the patient ingest enough of the placental proteins to cause a reaction through which the body's resistance will be augmented, both to them and to those produced within the patient. It does not involve any unknown fundamental of immunology and, "from a purely theoretical standpoint, should be entirely feasible," as one technician has said.

Each dose of Placenta Co.* consists of approximately 25 gr. of the parenchyma of fresh bovine placenta, freed of blood and as much connective tissue as possible, plus a minute dose of thyroid extract. This is put up in 5-gr. tablets. The usual minimum dose is 5 tablets a day, when convenient, with charged water or sedatives, and timed so as to be retained as fully as possible. Such treatment must be given for at least five consecutive days; and, in cases that bid fair to respond, it should be continued for at least three weeks, or for a full week after the vomiting has ceased.

This antianaphylaxis is brought about in the body itself—the remedy as such is useless, save only as it initiates a beneficial reaction on the part of the body cells; hence the need for applying it early. The results are quite different from those expected from drugs, and the treatment has absolutely no direct or sedative action.

LUTEAL HORMONE IMBALANCE—The foregoing method will be found to be ineffective in perhaps one-fourth of the cases. For this reason it is interesting to note that Hirst, Quigley, Hirshfield, and other workers suggest that the corpus luteum of pregnancy—which, by the way, is just as much a new organ as the placenta itself—is the chief source of the difficulty. John C. Hirst, of Philadelphia (*Am. Jour. Obst.*, March, 1919, lxxix, p. 327), offers the following explanation:

"Every woman, during the period of sexual activity, is constantly absorbing corpus luteum. No sooner is the corpus luteum of one menstruation disposed of, than another appears to take its place. With the onset of pregnancy, this absorption ceases. The corpus luteum of pregnancy constantly increases in size until it reaches its acme about the third month. From this time on, it is gradually absorbed. The nausea of pregnancy, beginning during the period of non-absorption, disappears about the time that the corpus luteum begins to decrease in size. Is it not reasonable to assume that this is not coincidence, but cause and effect, and that the corpus luteum plays an important part in relation to the nausea?"

Hirst recommends a solution of corpora lutea (1 cc.=0.2 Gm. of the desiccation), 1 or 2 cc. given intramuscularly daily for from twelve to fifteen doses. In pernicious cases the injections are given twice daily. In his article, Hirst reports ninety-nine successes in a series of 111 consecutive cases.

This idea has been used in our own failure cases with almost 100 per cent. results. So, since 1926 a compound solution, Placento-Luteum Co.,* has been employed, enabling us to combine these methods.

While I do not differ with Hirst's explanation of how his measure brings about its benefits, it is still within reason to suppose that exactly the same philosophy (of protein sensitization and the establishment of an immunity thereto) applies to the corpus luteum of pregnancy as the source of the offending protein instead of the placenta.

At any rate, these measures have astounded all who have had any extended experience with them and have added another dependable remedy to the list of organotherapeutic achievements.

In a later paper, Hirst (*Jour. Am. Med. Assn.*, March 19, 1921, lxxvi, p. 772) reemphasized the efficacy of this measure and urged the intravenous route, stating that anaphylactic reactions need not be feared. Nevertheless, not all agree that this method is superior to intramuscular injection. Personally I am opposed to the intravenous route when more than one or two doses have to be given. It has been found, however, as Hirst states, that "the presence of goitre in early pregnancy absolutely contraindicates the corpus luteum extract . . . every such patient has been made worse by this treatment." It might be added that placenta therapy, given by mouth to patients with hyperemesis and simple thyroid enlargement—not hyperthyroidism—frequently has been found to be beneficial both to the vomiting and to the goitre. It really seems that certain goitres are reactions to toxemia of this nature.

HEADACHE DURING PREGNANCY—Another phenomenon of pregnancy, probably often due to protein sensitization, is a type of protracted headache unrelated to hypothyroidism, liver toxemia (hypohepatism), or hypertension. It may or may not occur with nausea and vomiting.

Occasionally a patient with such a headache may be sensitive to the product of the fetal cellular breakdown. If so, nothing can be done directly. Indirect treatment, like that suggested for hepatobiliary insufficiency (104) and remineralization (100), should tend to support the patient's own presumably stressed detoxicating mechanism.

More frequently the sensitization is to the placental or luteal proteins. Placental protein sensitization may be determined accurately by my Placental Protein Test; and, in the presence of a positive reaction, a stubborn headache will often disappear under the same treatment as that outlined for hyperemesis—*i.e.*, Placenta Co.,* 5 or more tablets a day for at least ten days.

Again, there is a possibility of a true thyroid cause for such headache, especially in women with a previous history of thyroid defects. Here the headache disappears as if by magic when thyroid is given in insignificant doses.

It is presumed, of course, that the alimentary and other easily demonstrable causes of headache are ruled out before these essentially endocrine headaches are studied and treated.

TOXEMIAS OF LATE PREGNANCY—The hypertension of late pregnancy and the serious disorders that may follow it, such as eclampsia, undoubtedly are the result of a profound breakdown in detoxication. Although there is frequent evidence of renal involvement, the consensus is that the liver is the principal point of attack and that virtually always the kidneys are affected secondarily. The liver etiology has been confirmed quite definitely in three different ways: (1) The blood creatinine and uric acid are always high; (2) the van den Bergh or Rosenthal liver function test practically always shows poor elimination of the dye; and (3) there is a very high urinary acid index, increased ammonia, and low urea.

When Anabolin* was first made available for the treatment of functional high blood-pressure (13), several physicians used it in hypertension occurring in the last months of pregnancy. Early in the course of these clinical trials, the staff chief of seven physicians in the obstetrical department of a certain university tried Anabolin in many cases. His report was that "none of us has found it to fail to reduce prepartum hypertension." Since then, many hundreds of cases have been controlled in this simple way.

HEPATIC CAUSES OF ECLAMPSIA—It is now quite generally conceded that the toxemias of late pregnancy are caused by an interference with the hepatic detoxicative capacity, which now, fortunately, can be supported by the administration of the hepatic detoxicating hormone.

There are several theories regarding the origin of eclampsia, one of which was advanced by Stephen Rushmore, of Boston (*New England Jour. Med.*, April 4, 1929, cc, p. 700). Briefly his hypothesis is this: Eclampsia is attributable to a calcium deficiency in the mother, which affects the liver primarily. This produces increased permeability of the liver cells, with disturbance of their function and, histologically, results in a fatty degeneration or infiltration. If the damage is severe, necrosis of the liver may occur, in which event liver protein is thrown into the blood stream. This liver protein is toxic and may produce symptoms of anaphylactic shock; it is eliminated by the kidneys, producing marked albuminuria. The liver dysfunction may also cause hypoglycemia with convulsions and secondary changes in the

brain and liver. This theory explains the time occurrence of eclampsia, its prevention by modern prenatal care, the albuminuria, the occurrence of convulsions, and the similarity of some cases to anaphylactic shock.

Another stimulating suggestion showing the close connection between the liver and the toxemias of late pregnancy is made by Wilhelm Ortloph, of Munich, who believes that the pressure disturbances in the true pelvis produce obstructions to the venous flow (evidenced, for example, by hemorrhoids and varicose veins) leading to partial stasis in the sense of the reversed Eck experiment. A heavy overload is thrown upon the liver, and internal metabolism is difficult to regulate and maintain. According to this theory, the primary disturbance of internal hepatic metabolism is the underlying cause of nearly all disturbances during pregnancy, even the most violent toxemias. It is the impossibility of disposing in the maternal hepatic system of the fetal waste products that normally reach the vena cava that leads to such severe symptoms of toxemia, to coma, and death. But even in milder cases of intoxication it takes considerable time for the impaired liver tissue to resume its normal function.

The editor of *American Medicine* (Feb., 1931, xxxvii, p. 65) makes the following comment in discussing Ortloph's idea:

"Whether one wishes to go all the way with Ortloph or not, it seems evident from his work that integrity of hepatic function is perhaps the most important factor for the prevention of infection during pregnancy and the puerperium. That such severe ketoses can occur as a result of damage to the liver seems evident; or, to put it more simply, dangerous predisposition of the organism to toxemias and puerperal sepsis is a direct and inescapable result of hepatic impairment."

My own theory is that this stress on the liver interferes with its power to fit together completely the precursors of the nitrogenous wastes. These substances, chiefly guanidine and its congeners, are allowed to pass into the general circulation. Being decidedly pressor in nature, they raise the blood-pressure. Some of these half-formed protein-split products may act directly upon the renal glomerular and hepatic parenchymatous epithelia causing an anaphylactic-like swelling and impermeability that mechanically interfere still further with the corresponding function.

CLINICAL SUCCESS WITH LIVER EXTRACTS—There are a number of interesting clinical reports. H. A. Miller and D. B. Martinez (*Am. Jour. Obst. and Gynec.*, Aug., 1927, xiv, p. 165) report on fifty cases of pregnancy toxemia, including seven of eclampsia, that were treated with Heparmone. No dietetic or other intervention was advised, except in patients who

showed a blood-pressure of more than 180. The symptoms began to abate a few hours after the first injection, and pregnancy continued to delivery without toxic symptoms. Convulsions did not occur in any preeclamptic cases, and there were no ill effects. It may be said, however, that renal damage interferes definitely with this therapy. Eleven of this series of patients who had "preconceptional nephritis" were only symptomatically improved following the use of the liver extract; three such cases did not respond to it at all. The following statements are quoted from the Miller-Martinez paper:

"The rapid abatement of the symptoms is noteworthy. Headaches, dizziness, spots before the eyes, epigastric pain, rapid pulse, nervousness, and coma disappeared in the course of a few hours. The edema of the extremities and face disappeared in a few days. . . . The urinary output increased, the albumin decreased in amount and in some cases disappeared entirely. . . . Blood chemistry gradually improved. . . .

"In the past we accepted certain evidence of toxemia as an indication for the induction of labor or even cesarean section. The present consecutive series are all continuing their pregnancies, free from toxic symptoms and with normal blood-pressure, or have gone into labor spontaneously and have been delivered."

More recently these same authors (*Jour. Am. Med. Assn.*, Feb. 23, 1929, xcii, p. 627) report on a total of 255 cases of preeclampsia, of which 101 were classed as mild, ninety-five as moderate, and fifty-nine as severe. These were given Heparmone intramuscularly—the mild cases, 10 cc. weekly; the moderate ones, 10 cc. two or three times a week; and the severe cases 10 cc. two or three times daily until delivery. No other treatment was given. Of the forty-three cases of eclampsia that these workers treated between October, 1926, and June, 1928, only three died, a mortality rate of 6.9 per cent. However, they do not consider the value of the method to be definitely established.

In a series of reports on 150 cases of hypertension that J. D. Willis treated with Anabolin* (*Virginia Med. Month.*, Sept., 1930, lvii, p. 361), it appears that this writer was able, almost without exception, to bring about symptomatic relief and a marked reduction in blood-pressure. Speaking specifically of Anabolin, he says, "It is unquestionably of value in the treatment of toxemia of pregnancy and preeclampsia."

The following interesting report was published in 1929:

"A girl, 17 years of age, gave birth to twins. The delivery had to be made by cesarean section, and eclampsia followed. The usual measures, including magnesium sulphate, failed, and the patient had twelve convulsions. (B. P. 174/110, albumin ++++.) An intramuscular injection of 2 cc. of Anabolin Solution was then given. The doctors were surprised and pleased at the

apparently prompt response (a second similar injection of Anabolin was given six hours later). She had no more attacks after the first injection was given, and made an uneventful recovery. Two and a half years later there was no evidence of kidney damage."

Inasmuch as the toxemias of late pregnancy involve chiefly the liver, and inasmuch as this hepatic hormone is a direct means of hastening hepatic detoxication, it would seem that it might reasonably be called a specific in this type of case.

Many physicians who have had an extended experience with Anabolin are in the habit of prescribing Anabolin tablets—1, 2, or 3 a day with food—as a routine prophylactic measure during the last two, three, or four months of pregnancy. The dose and the time to initiate treatment depend entirely upon the patient's previous history.

MAMMARY TOXEMIA IN ECLAMPSIA—Due largely to the efforts of Bertha Van Hoosen, of Chicago, a new phase of the toxemias of pregnancy is being emphasized. In an address before the Chicago Medical Society (*Bull. Chicago Med. Soc.,* Feb. 7, 1931, xxxiii, p. 23), this writer refers to a method that she had described at the Pan-American Congress, in January, 1930, for making a differential diagnosis between hyperthyroidism, the nephritides, and the toxemia of pregnancy. This procedure, by the way, furnishes additional clinical evidence for the idea that mammary disturbance may be a factor in this toxemia. The colostrum is stripped from the breasts of the hypertensive patient, and at the end of an hour the blood-pressure will be reduced from ten to fifty points if the patient is suffering from toxemia of pregnancy. In the presence of nephritis there will be little or no reduction, and in hyperthyroidism a slight reduction. This method has been employed successfully in more than two hundred cases of hypertension.

In attempting to explain the prompt reduction in blood-pressure, this question arises: What is the substance in the retained colostrum that causes the blood-pressure to rise in certain cases? Van Hoosen refers to a report by Johnson, of Houston, Texas, who had found tyramine in the blood of eclamptic patients. The colostrum was examined for this substance, and the early results encouraged further research. Of thirty-three specimens of colostrum thus tested, twelve came from patients in whom the delivery and blood-pressure were normal. In none of them was there a trace of a tyramine-like substance. In one case of eclampsia, however, such a substance was found in the colostrum in both breasts, but a second specimen taken two days later showed a reduction. One week after the first specimen, a third

one was taken, and only a trace of this tyramine-like substance was found. Other cases showed similar findings, justifying the conclusion that a tyramine-like substance is present and disappears slowly in severe eclamptic cases. No such reaction was noted in normal cases. Further confirmatory work is required, but no harm can come from the clinical application of this idea in patients with increased tension during pregnancy, and whose breasts contain colostrum.

DELAYED LABOR—The discovery by H. H. Dale, of London, that a musculotonic pressor fraction could be separated from the posterior lobe of the pituitary, and the establishment of its clinical value by W. Blair Bell, of Liverpool (1908-1909), have revolutionized obstetrics just as other equally wonderful advances in endocrinology have revolutionized several other phases of medicine (18).

The oxytocic product known originally as Infundibulin, and more aggressively promoted in this country as pituitrin, has proved of the greatest value because of its stimulating influence on the parturient uterus. Pituitrin stimulates uterine contractions, thereby hastening delivery and preventing postpartum hemorrhage. As with every advance in medicine, a plethora of articles, both clinical and critical, has appeared; and opinions vary widely. It may be said, however, that the use of liquor pituitarii, as it is known in the U.S.P., is now an accepted routine measure, and the main differences of opinion have to do with the dosage and time of its administration.

Small doses of from 3 to 5 min. of the so-called "obstetrical strength" (each cubic centimeter of which contains 10 international units), given intramuscularly and repeated at 15-minute intervals, are preferable to one dose of 1 cc. All concede that posterior pituitary extracts must not be given in the first stage of labor nor in the presence of an obstruction.

During the last few years a new idea that originated in Europe has gradually been establishing itself in this country. Nikolaus Temesváry, of Breslau (*Zentralbl. f. Gynäk.*, Feb. 6, 1926, I, p. 322), found that a combination of the thymus and the posterior pituitary principles called Thymophysin, modifies the character of the uterine contractions and causes them to be intermittent rather than continuous. This is reported to have been used in an extensive way at the very onset of labor, and, although it has been hard to accept so radical a change, it appears to be a real advance. Thymophysin has the advantage of earlier administration; then, too, it does not exert so marked a pressor effect as does pituitrin. The change in the nature of the stimulation from a prolonged contraction, thus ————————, to a series of broken contractions, thus —— —— ——, has not yet been satis-

factorily explained; but many writers are enthusiastic in their praise of the combination. It retains the acceptable pituitrin stimulus, while tending to maintain the normal non-tetanic rhythm and regularity of the contractions. Two such products are available: Thymophysin and Pituthymin.* M. Davis, of Boston (*New England Jour. Med.*, Oct. 16, 1930, cciii, p. 771), reports the use of Thymophysin in fifty carefully studied cases. He concludes:

"(1) Thymophysin can be given as soon as regular labor is established; (2) there is apparently no danger of tetanic contraction of the uterus; (3) it definitely shortens labor; (4) it can be given for secondary inertia of the uterus, if the patient is not too fatigued; (5) the preferable dosage is 0.5 cc. repeated in from forty-five to sixty minutes; (6) there seems to be no danger of injury to mother or child; (7) with careful watching, it can be used to give a good trial of labor to borderline cesarean cases; (8) it does not seem to be effective in inducing labor, hence it can be used to differentiate true labor from false labor."

DYSTOCIA DUE TO INFILTRATION—There are two endocrine dystocias that respond to organotherapy. Both are due to hypothyroidism, which in the one produces an abnormally large fetus, and in the other an infiltration of the soft tissues of the birth canal. Manifestly, both conditions often exist together.

To the reader who appreciates the degree to which the cells can become infiltrated as a result of hypothyroidism, the reality of these conditions will be obvious. Naturally, they are always due to long-standing defects culminating in maximum endocrinopathy.

The best treatment is prevention by early thyroid therapy. Indeed, there is no other. The therapeutic possibilities are purely prophylactic.

Too often the thyroid values in pregnancy are overlooked. We should remember that hypothyroidism is almost exclusively a woman's disease, is very common in pregnancy, and is a potential cause not only of the comparatively rare disorders referred to here, but also of the more important endocrinopathic inheritance transmitted to the offspring, which has been discussed previously (46).

85. PROSTATIC HYPERTROPHY

The Male Climacteric—Compensatory Hypertrophy—Lydston's Ideas on Sexual Neurasthenia—Clinical Experiences—Prostatic Organotherapy.

THE PHILOSOPHY underlying the following suggestions includes two points that are not yet generally accepted as facts: (1) that the prostate is a gland of internal secretion, and (2) that there is such an intimate functional relationship between the prostate and the testes that waning gonad activity arouses a compensatory cooperative activity of the prostate.

There is now little question about the first premise, but the reader is directed to a collection of data (20) which should be convincing evidence that the prostate is a part of the endocrine mechanism.

The second premise is not difficult to establish. Fortunately clinical confirmation is not only possible, but comparatively easy; and it happens that I am in a particularly good position to judge, for I have been in personal contact with more than seven hundred physicians who have suffered from the discomforts of prostatic hypertrophy and who have used their own cases as clinical material on which to test this theory.

THE MALE CLIMACTERIC—Let us go back a bit and establish a background for these empirical, clinical accomplishments: Several authors have expressed the opinion that it is as possible for a climacteric to take place in men as in women, and they consider that many of the neurasthenic symptoms observed in men around the age of fifty often can be compared with the menopausal findings in women. Indeed, Louis Berman, of New York ("The Glands Regulating Personality," New York, The Macmillan Co., 1921, p. 163), says:

"Man has his critical age of sex cell deterioration as well as woman. The age chart swings between forty-five and fifty-five. Here enters upon the scene that organ of external and internal secretion, the prostate, the most important accessory sex gland in the male. . . . Furthermore, the microscope reveals cyclic changes in those cells comparable to the menstrual phenomena of the uterus. . . . The regression of the prostate is the central episode of the male climacteric."

While men may not experience the hot flushes that women have during this period, they often suffer from constipation, headache, malaise, loss of appetite, loss of strength, lack of sexual power, insomnia, and other symptoms that make up a neurasthenic syndrome. Since ovarian substance is of value in the female climacteric, why might not prostatic substance be beneficial in men presumed to be deficient in the internal secretion of the prostate at the

corresponding period of life? Clinical application shows that this query may be answered in the affirmative.

COMPENSATORY HYPERTROPHY—We must remember that, because of the definite relation between the testes and the prostate, it is probable that the prostate often hypertrophies after removal of the testes, evidently as a temporary compensatory reaction to make up for the lacking gonad internal secretion. Fundamentally this is the same as thyroid enlargement during a period of ovarian insufficiency, or pituitary hypertrophy as an attempt to meet a lack that it cannot supply.

In 1918 I suggested to my friend, Victor G. Vecki, the San Francisco urologist, that, if the foregoing premise is sound, Leydig-cell stimulation should be a reasonable treatment for simple (non-surgical) prostatic hypertrophy, especially when the gonad function is waning. Since that time, several articles have been published embodying similar ideas regarding compensatory prostatic hypertrophy. Whether the hypothesis is right or wrong, the treatment suggested has been clinically efficacious time and again.

A London urologist, F. Howard Humphris (*Lancet,* Aug. 4, 1928, ccxv, p. 221), agrees with the idea of cell equalization. He says:

"The fact that prostatic hypertrophy quite commonly follows the functional retirement of the testes, has caused many observers to believe that there is some relationship between the endocrine activities of both these glands. It is believed that when the testes become functionally inactive the prostate becomes enlarged in a compensatory fashion, just as other ductless glands enlarge when closely related glands are put out of commission. It is generally accepted that, when deep-seated infective processes and essential new growths of the prostate gland can be excluded, there remains a form of enlargement of the prostate gland which is closely related to waning gonad function. This should theoretically respond to treatment by organotherapy, which would supplement the endocrine function of the testes and thereby lessen the probable necessity for overactivity on the part of the prostate."

It was observed by G. Guelpa, of Paris (1922), that men engaged in certain types of intellectual work, whose sexual activity has been arrested, show a predilection toward prostatic enlargement, while in tribesmen whose customs allow polygamy and little mental strain there are but few cases of enlarged prostate. This writer also expresses the opinion that has been hinted at elsewhere, namely, that the uterus and the prostate are analogous organs, and that early cessation of sexual activity is liable to cause enlargement of the prostate. It is interesting to note that Guelpa considers uterine fibroids to be most common in nulliparæ; and, since we are to consider the prostate as a male uterus, its disease should appear more often in inactive glands.

LYDSTON'S IDEAS OF SEXUAL NEURASTHENIA—In his book, "Impotence, Sterility, and Sex Gland Implantation" (Chicago, The Riverton Press, 1917, p. 200), the late G. Frank Lydston, of Chicago, has given some very important facts relating to sexual neurasthenia and prostatic dysfunction. His extended clinical experience led him to conclude that neurasthenia in the male is often secondary to prostatic disturbances, including inflammation of the prostatic urethra and hyperesthesia of the verumontanum. He says:

". . . the prostate secretes a hormone, the perversion of which, conjoined with the absorption of infection toxins, often has much to do with the etiology of sexual neurasthenia.

"Disturbed digestion, irregular bowel action, headache, depression, lassitude, melancholy and brooding, hypochondriasis, introspection, unstable emotions, and 'hysteria'—for there is a condition in the male analogous to hysteria which we logically might call 'prostateria'—are among the results of a sensitive, congested prostate and deep urethra."

To carry further the suggested analogy between the prostate and seminal vesicles on the one hand, and the uterus and tubes on the other, Lydston recalls the fact that infected tubes and uterus with the surrounding pelvic infiltration produce pressure and neurasthenic symptoms; likewise, inflamed seminal vesicles (periprostatic infiltration) produce disturbances that may develop into general nervous symptoms. The chronic, long-drawn-out course of both conditions is well known. Vincent makes some encouraging statements about prostatic organotherapy to the effect that he has several reports that apparently demonstrate advantageous results following the administration of prostatic substance in suitable cases.

In speaking of the experiments of Camus and Gley, who found that seminal fluid produces more active spermatozoa when a small amount of prostatic extract is given, Arnold Lorand, of Carlsbad ("Old Age Deferred," Philadelphia, F. A. Davis Co., 1920, p. 445), says:

"Thus it is very probable that, by adding prostatic extracts to those of the testes, the vitality of such extracts may be enhanced."

P. Lereboullet *et al.*, in their book, "Endocrine Glands" (translated by F. Raoul Mason, Philadelphia, J. B. Lippincott Co., 1922), refer to the utility of prostatic extracts in neurasthenia of sexual origin, and state that it is in "neurasthenia that dry prostatic extracts give appreciable results."

CLINICAL EXPERIENCES—In the *American Journal of Clinical Medicine* for March, 1920 (xxvii, p. 180), Malford W. Thewlis, of New York, reports a case of senile prostatic hypertrophy. His patient, 70 years old, complained of frequency of urination, especially at night. He experienced considerable pain and difficulty before and during micturition; in fact, the

prostatic obstruction was so great that it became necessary to catheterize him with a metal catheter. Examination of the prostate and urinalysis revealed the fact that he was suffering from prostatic hypertrophy and chronic nephritis. A dietetic régime was instituted, general tonic treatment was employed, and prostatic extract was given by mouth every three hours. The patient was relieved on the second day, and catheterization soon became unnecessary. Improvement was marked from the very start, and within a week the patient had returned to practically normal senility. Thewlis has observed the same beneficial results from the oral use of prostatic extract in a number of other cases; this therapy not only relieves the prostatic condition, but also removes many distressing symptoms of a neurasthenic nature attendant upon this condition.

In the treatment of prostatic conditions, the German writer, H. Rohleder (*Deutsch. med. Wchnschr.*, Jan. 15, 1920, xlvi, p. 70), employed a pluriglandular preparation containing testicular extract, prostatic substance, and an extract from the seminal vesicles. His first pluriglandular preparation contained yohimbin also, but this irritant was discontinued since it did not in any way increase the efficacy of the other substances. Rohleder reports two cases that are worth our attention: The first was that of a man of 75 years who had been "a prostatic" for about fifteen years and who for the last eleven years had endured chronic cystitis, nephritis, and, of course, urinary retention. He had been forced to catheterize himself three times a day, had tried sitz baths, had avoided alcohol and other irritating substances, and had had bladder irrigations with silver nitrate (1:1000). Because of his age and general condition, prostatectomy was contraindicated. Rohleder required this patient to take the pluriglandular formula mentioned above regularly three times a day for two weeks. A complete cure was not realized, but the painful micturition and many other distressing symptoms were relieved.

The other case was that of a man, 70 years old, who for four months had suffered from an enlarged prostate with cystitis, cloudy and residual urine, and dysuria. He also was given pluriglandular therapy. After twenty days there was little difficulty in urination, no residual urine, and no cloudiness. After two more weeks of treatment there was additional improvement. However, when the treatment was suspended all the symptoms returned.

Rohleder draws several conclusions: (1) Yohimbin is not necessary in pluriglandular preparations for the treatment of prostatic irregularities; (2) pluriglandular formulas produce the best effects when used in the early stages of prostatic hypertrophy, *i.e.*, when there is yet no residual urine, only

a difficulty in urination; and (3) although the results from organotherapy are not permanent, they are beneficial and often relieve conditions in inoperable cases. He does not hold out much hope for the late, so-called "third-stage" prostatic hypertrophy.

D. F. L. Martinez (*Progresos de la clin.*, July, 1922, x, p. 52) has tested this same treatment in several patients, all of whom were relieved. The first, age 75 years, had been the usual rounds in the attempt to find a cure. He finally called Martinez to his home because of complete retention of urine, and four liters were removed by catheterization. Examination revealed no other stricture than urethral compression caused by the pressure of the hypertrophied prostate, which was very sensitive. Catheterization was repeated on the two ensuing days, then organotherapy was begun and almost immediate relief followed. At the end of a month the patient passed large amounts of urine freely. Now, after two years, he still continues the endocrine treatment and is in good health.

The second patient was 76 years old. The details of his condition were similar to those in the first case, except that the urine contained a great deal of pus. The same treatment was administered and the same beneficial results were obtained, although two months were required to get complete relief.

The author reports other cases in patients around 75 years of age, all of whom presented the same symptoms. All received pluriglandular treatment, which produced either a cure or definite relief from the major symptoms.

Finally, it may be recalled that H. Lyons Hunt, of New York (*Endocrinology*, Nov.-Dec., 1925, ix, p. 479), submitted the thesis that the testicular hormone is not entirely responsible for the functions attributed to it and that the prostatic internal secretion shares in them, as is demonstrated by the results of prostatic organotherapy.

PROSTATIC ORGANOTHERAPY—After considering the experimental and clinical possibilities of prostatic substance, it was decided to add it to the Leydig-cell product already in use. Each sanitablet of the modified preparation called Prostate Co.* contains equal parts of a desiccated prostate concentrate and spermin extract (interstitial cells of Leydig), and an effective dose of nucleic acid. The latter is added because of its leukocyto-stimulant effect and its well-known value in increasing the resistance of those who have been depleted by infection. The Leydig extract is added for its synergistic homostimulative effect on the gonads, its evident relation to the testes and the prostate, and its tonic effect.

The usual dosage of this formula is 1 sanitablet before meals and at bedtime. In severe or advanced cases, it is wise to double this dose for

occasional periods of from two to four weeks. There is no detrimental reaction to the treatment, and, although results may appear quite promptly, a month or more often elapses before definite progress is noted. This treatment must be continued for at least four consecutive months, especially in elderly men.

It may be well to report a few clinical cases. The first has been mentioned in "Practical Organotherapy" (1922, p. 213): The patient, a physician 81 years of age, came to me in the hope that I might relieve him, for he had undergone long periods of treatment of various kinds with no relief. Examination and history showed that he had a greatly enlarged prostate, the resultant urinary difficulty, and an extremely obstinate constipation. He was very old, his health was impaired, his heart was not functioning properly, and we felt that surgery undoubtedly would cause his death. I told him to use Prostate Co.,* although I assured him that there was not much prospect of a recovery. He reported later in the following words:

"I am much better. The difficulty with urination is gone, and, with the exception of two or three short intervals, I have had no trouble with dysuria and frequent micturition."

With the subjective improvement there was also a decided reduction in both the size and the tenderness of the prostate, and my old friend lived in comfort for more than three years until the grim reaper caught him.

The story of the seven hundred would be a fitting conclusion to these comments but there is not space for it. It just happened that in 1928 I made an effort to get in touch with as many physicians as possible who themselves were suffering from prostatic hypertrophy. I did this in order to demonstrate to them the possibilities of prostatic organotherapy. More than seven hundred physicians have personally tested this method, and I have clinical records from hundreds of them which confirm me in my faith in this empirical form of treatment, despite a statement to the effect that "until a true active principle is secured from the prostate, and its identity and potency are established, such treatment cannot be accepted." This is exactly what was said about several other forms of organotherapy before the whole truth was revealed, and it is predicted that history will repeat itself and that some day the present reticence in some quarters will be replaced by the same enthusiasm that one now finds for pancreas therapy in diabetes, liver therapy in anemia, and parathyroid therapy in ulcer.

86. RENAL DISEASE

Nephritis—Anuria—Glomerular Nephritis—Thyroid in Nephritis—Lipoid Nephrosis.

MEDICAL THOUGHT did not accept the idea of an endocrine basis of renal disease until Hans Eppinger, of Vienna, reported relief from stubborn edemas by the use of thyroid extract ("Zur Pathologie und Therapie des menschlichen Oedems, zugleich ein Beitrag zur Lehre von der Schilddrüsen-funktion," Berlin, J. Springer, 1917). This empirical success caused other workers to suspect that there might be an endocrine factor underlying some types of kidney disease. But prior to this, James F. Percy, now of Los Angeles (*Jour. Am. Med. Assn.*, Nov. 9, 1912, lix, p. 1708), had made "a preliminary statement of a new and effective method of treatment" in nephritis. Further attention will be given to his reports.

NEPHRITIS is a term used to indicate several quite different ultimate conditions, few of which are clearly defined. The picture to-day differs very materially from that of twenty-five years ago. For example, the interstitial nephritis then commonly discussed is no longer considered a clinical certainty. The essentially constitutional character of certain nephritides leads one to a consideration of the regulators of constitution—the endocrines—and it is surprising how decided is the trend toward an endocrine conception of both the susceptibility to, as well as the actual cause of, several of the common renal diseases.

ANURIA—Since the cause of anuria usually is a serious, organic one, it is frequently a prelude to the inevitable. Through its effect on the blood-pressure, epinephrine is effective in temporarily restoring defective kidney function. J. S. Lankford, of San Antonio, Texas (personal communication), tells of having seen fourteen cases in which the suspension was complete, and in all of which he used adrenalin with success. The dose recommended is 8 min. of the 1:1000 solution given by intramuscular injection every hour to effect.

Rarely, the renal function may be interfered with following an injection of Anabolin,* especially if the hypertension for which this product is used is renal and mechanical rather than hepatic and purely functional. The resulting anuria is not serious, and treatment consists of the discontinuance of Anabolin, the administration of much water, fruit juice, and, if desired, potassium citrate. This type of anuria is purely mechanical in character, the reduction in the blood-pressure causing insufficient pressure to overcome the

interference in the glomeruli. Such an experience (about fifteen cases have been reported in the last six years) is of decided differential diagnostic value. In these cases a renal efficiency test (with phenolsulphonephthalein) should have been made first.

Anuria sometimes accompanies major hypothyroidism, due presumably to glomerular infiltration (67), and has been controlled promptly by immense doses of thyroid. As we shall soon see, J. F. Percy made a noteworthy contribution to the treatment of maximum degrees of renal impermeability by showing that thyroid therapy can be used with definite benefit in many cases in which suppression of urine is one of the factors to be overcome.

GLOMERULAR NEPHRITIS is the true type of inflammatory renal reaction which, starting from the irritation of the internal structure of the essential functioning tissue of the kidney (the glomeruli), eventually may involve the other structures. This condition is not directly susceptible to endocrine therapy, although in diatheses of known endocrine antecedents the control of the underlying dyscrinism obviously would spare the renal structure as, for example, in hypothyroidism.

Since *perméabilité rénale,* as the French call it, is dependent upon a normal status of the endothelial linings of both the glomerular capillaries and capsules, any factor damaging those linings will interfere mechanically with this permeability. While it is not generally acknowledged, the infiltration of hypothyroidism, to which attention has been called (67), affects these endothelial structures in exactly the same way as it affects other cells—they become puffy, swollen, and infiltrated, thus interposing a mechanical interference to the normal exchanges from the blood to Bowman's capsule. Capillary permeability, believed to be of vital importance in many other edematous conditions, may be a predisposing element in the causation of glomerular nephritis. Certain it is that this is involved in the less common condition known as lipoid nephrosis (*q.v.*).

One may conclude, then, that the patient with glomerular nephritis may have, with the actual kidney lesion, an associated cellular predisposition which, if appreciated, might also be modified with advantage.

THYROID IN NEPHRITIS—In 1912, James F. Percy (*Jour. Am. Med. Assn.,* Nov. 9, 1912, lix, p. 1708) reported on the clinical value of thyroid therapy in nephritis. Thirty-five cases were remarkably benefited by huge doses of thyroid extract—from four to ten 5-gr. tablets a day. His interest in the subject originated in connection with his study of a case of goitre with nephritis. He concludes:

"I am quite certain that, speaking generally, we can now add nephritis to the large list of cases brought to the internist suffering from hypothyroidism."

Percy adds some interesting historical data that seem to have escaped attention, and then proceeds:

"After my faith in this treatment of nephritis had reached the stage of conviction, it dawned on me that, with the almost universal use of the thyroid gland in so many widely divergent conditions, some investigator had also certainly made use of it in Bright's disease, and learned of its value. With this in mind, I asked the Surgeon-General's office at Washington to search the literature, with the result that only one contribution was found that had any bearing on the use of the thyroid gland in the conditions under discussion.

"In the *Archiv für experimentelle Pathologie und Pharmakologie* (1897, xxxix, p. 273), I found a most valuable and interesting article by G. Diaballa and von Illyés entitled 'Researches on Metabolism in Bright's Disease while Feeding Thyroid Preparations.' This experimental work, done fifteen years ago, has evidently been buried in this special journal all these years. The purpose of the authors seems to have been simply to demonstrate that any individual suffering from Bright's disease—and many other diseases—would, if given the extract of the thyroid gland, show an increased diuresis and an increased excretion of urea. Their experiments showed that this was true also in the healthy adult, but it was not true when this substance was fed to the young. Nowhere in the published record of their work do these investigators seem to have conceived the idea that the administration of the thyroid gland would favorably influence the protean progress of the symptom-complex which has been designated so long as Bright's disease."

LIPOID NEPHROSIS—The association of dyscrinism with kidney disease is most striking and indisputable in lipoid nephrosis. Thyroid extract and protein food (both means of stimulating intracellular metabolism) constitute the treatment. Thyroid deficiency may form part of the etiology, and must be considered in the diagnosis.

Albert A. Epstein, of New York (*Jour. Am. Med. Assn.*, Sept. 18, 1926, lxxxvii, p. 913), defines nephrosis (sometimes known as Epstein's nephrosis) as a type of chronic tubular nephritis resulting from systemic metabolic disorder occurring usually in young persons and in women, and frequently associated with endocrine disturbances. Epstein distinguishes between myxedema and nephrosis thus:

"The distinction might be clarified by designating myxedema as an actual hypothyroidism and chronic nephrosis as a relative hypothyroidism."

The explanation is made by Epstein that nephrosis is not a result of pathological changes in the thyroid gland as one finds in myxedema, but that the

activity of the thyroid in these cases, whether normal or even increased, "is insufficient to cope with the existing metabolic disturbance."

In a consideration of commonly overlooked results of hypothyroidism, James H. Hutton, of Chicago (*Clin. Med. and Surg.*, Nov., 1927, xxxiv, p. 825), refers to this as follows:

"Thyroid deficiency frequently produces a syndrome very closely resembling nephritis. As a matter of fact, these cases are very frequently diagnosed nephritis, and treatment is directed along those lines. The color of the skin, the edema, the increase in blood-pressure, the presence of albumin and casts in the urine, and even some retinal changes form a reasonable basis for the diagnosis of nephritis.

"The kidney disturbance now known as nephrosis, for lack of a better name, is accompanied by a lowered basal metabolic rate and is greatly benefited by thyroid medication. There is as much reason for classing this as a hypothyroid disturbance as there is for calling it a kidney disease. True, there are some pathologic changes, probably in the kidney, but there is certainly a deficiency of thyroid function."

The clinical picture of this condition is especially important in view of the hope that it may offer to nephritics whose prognosis may be changed entirely by applying this newer knowledge.

The onset of the difficulty may date from an attack of acute glomerulonephritis, but usually it is insidious. There are loss of appetite, fatigue, pallor, edema, albuminuria. The quantity of urine is diminished; the specific gravity, however, is usually normal; albumin is present (from 5 to 20 Gm. per liter); hyalin and granular casts are found, but there is no hematuria. Edema begins in the ankles and eyelids, and gradually spreads; or a quite generalized edema may be marked from the first. There is edema of the gastro-intestinal tract, which may be the cause of diarrhea.

An increase in the blood-pressure is unusual, and cardiac hypertrophy is rare. The cholesterin content of the blood is increased; the total protein diminished. Serum globulin is increased, and serum albumin is decreased. Non-protein nitrogen, urea, uric acid, and creatinine are not increased. The renal function tests show no renal insufficiency. The basal metabolic rate is routinely low—usually from minus 17 to 19 per cent.

The outstanding peculiarities of this condition are the normal blood-pressure, average renal efficiency, and low basal metabolic rate, with a picture otherwise quite like true nephritis.

The patient often dates the beginning of this disease from a pregnancy. No causal relationship between pregnancy and lipoid nephrosis has been established, although it is now believed that the kidney of pregnancy is really a form of nephrosis.

The present idea is that the fundamental change is an intracellular disturbance of nutrition, not localized in the kidney but generalized throughout the body. Epstein, thinking that this was a perversion of protein metabolism comparable with the perversion in carbohydrate metabolism in diabetes mellitus, designated the disease *diabetes albuminuricus*.

Endocrine disturbance, especially as a cause of the edema, is much more than a fascinating possibility. In fact, Krogh has demonstrated a hormone control of the permeability of capillary membranes, which are the dividing membranes between fluids entering and leaving the blood. The conclusion was that the hormone regulating this function is in the internal secretion of the intermediary portion and the posterior lobe of the pituitary. Incidentally, Pohle, Jungmann, and Bernhardt removed the neural part of the pituitary in frogs and noted post-operative edema in the legs and abdomen, with increase in weight.

Credit usually is given (erroneously, as I have shown earlier) to Hans Eppinger, of Vienna, for introducing thyroid extract into the treatment of what is now called lipoid nephrosis. At first he used it to relieve the various forms of edema. Here is his reasoning: In Graves' disease the skin is elastic, its circulation good, and there is very little predisposition to the formation of edema. In myxedema, on the other hand, the skin is dry and thick with an edematous appearance. Eppinger wondered whether persons with a mild form of constitutional hypothyroidism might not be especially predisposed to edema, and whether thyroid extract might not benefit patients that are resistant to other diuretics. He obtained his best results in cases of lipoid nephrosis, some of which were associated with nephritis. When he published his results he did not know that the basal metabolic rate is consistently reduced in lipoid nephrosis. Undoubtedly the effect of thyroid extract in reducing this edema, as in infiltrations elsewhere, is through a generalized increasing of the cellular metabolism.

We now presume that Percy's patients had nephrosis rather than nephritis. The distinction may be only in name, for, while Epstein (1922) insists that nephrosis is not nephritis, E. T. Bell, of the Mayo Foundation, in his recent paper (1931) before the California State Medical Association convincingly disagrees with this position. It is immaterial whether it is nephritis or nephrosis—the same thing or different—what we do know is that endocrine therapy offers some real prospect of benefit in certain apparently serious renal syndromes, and once more organotherapy adds to its many laurels.

87. RHEUMATISM

Thyroid Rheumatism—The Clinical Test Advised—An Ovarian Type of Rheumatism—Adrenal Control of Muscular Chemistry.

As WITH neurasthenia, so with rheumatism—it is often "a cloak to cover our shortcomings in diagnosis." Muscular rheumatism, sometimes called "myositis," is the result of a toxemia involving the chemistry of the muscles especially. It must be considered from the standpoint of the endocrine glands, therefore, because they are responsible for the cellular chemistry generally and for the muscular chemistry in particular.

THYROID RHEUMATISM—Some years ago, after a visit to Paris, during which I had the opportunity to see a number of cases of chronic rheumatism in the clinic of my friend, Léopold-Lévi, the importance of the thyroid aspect of rheumatism was impressed upon me. The patients were employees of the Métropolitaine, women ticket sellers (most of them at or near the menopause), who had to sit in the drafty entrances to the underground stations. Some of their rheumatic manifestations were so obviously endocrine in character and so satisfactorily controlled by the indicated treatment—usually thyro-ovarian organotherapy—that, on my return to America, I made a special study of the subject and published my findings in *American Medicine* (June, 1915, x, p. 363). A number of points from that article may be reiterated here:

None can deny that one of the most constant manifestations of the majority of cases of rheumatism is a disturbance of metabolism, even though many chronic rheumatic affections are of focal bacterial origin. It is remarkable how close the relation is between certain ductless glands and the symptoms that are considered pathognomonic of rheumatism. Presuming for a moment that the various symptoms of the rheumatic diathesis are of toxic origin, is not detoxication controlled by certain endocrine glands?

If infections are admitted to be the most frequent or important cause of rheumatism, then we must also admit that some of the endocrines are responsible for the production of the protective measures that the body automatically brings into play in infection (68).

In the introduction to his book, "La petite insuffisance thyroïdienne et son traitement" (Paris, O. Doin et Fils, 1913, p. 8), Léopold-Lévi remarks:

"Therapeutics is very helpful in the study of minor hypothyroidism, for it reveals several stigmata of this condition that otherwise might be overlooked. For example, in March, 1905, we made the first application of thyroid therapy, aside from its use in the treatment of myxedema, in a subject

suffering from chronic rheumatism complicated with psoriasis. The first noted effect consisted in an increase in the appetite; the second result was a reduction in the marked feeling of cold which happened to be present (this sufferer was astonishingly cold and lived in a degree of heat that was altogether preposterous). Strangely enough, the thyroid therapy produced a decided diminution in this peculiarity and also benefited the rheumatism. This form of treatment having been applied in other cases of chronic rheumatism, our attention was directed to its benefit in constipation."

Chronic rheumatism is quite common in subjects presenting signs of hypothyroidism, and it is well known that it may be associated with or aggravated by incidents in the climacteric, during which thyroid disorder is unusually frequent. Rheumatic manifestations often follow thyroid atrophy caused by pathological conditions or following thyroidectomy for Graves' disease.

The physician who has learned by experience of this relationship will quickly agree with Lévi (*ibid.*, p. 211) that

"The reality of the thyroid causes of chronic rheumatism is incontestable. Its existence depends in many cases on thyroid lesions."

THE CLINICAL TEST ADVISED—It is difficult to state definitely which cases of rheumatism are of thyroid origin and which are not. According to Lévi and de Rothschild, the only way to decide is to apply thyroid extract empirically. They say:

"From the practical point of view, in all forms of rheumatism in which the cause is unknown, it is an advantage to apply thyroid therapy. In such cases there will be more chance of results if the subject is young, if the rheumatism is accompanied with subacute exacerbations, and if there is only slight deformity. In those cases in which there is a decided thyroid influence, the initial results will be rapid and sometimes immediate. If the treatment does not act immediately, it is advisable to vary the dosage, sometimes reducing it and giving the remedy for a longer period. There is no doubt that this medication may render very great service in the treatment of certain rheumatics without exposing them to the least danger."

Of course, as has been remarked, Léopold-Lévi looks at every disease from the standpoint of its relation to the thyroid gland—he has been called "thyroid mad"—but the fact remains that he and his associate, Baron Henri de Rothschild, have treated hundreds of cases successfully with thyroid. In a later communication, Lévi reports on three hundred cases that had been treated under his direction during a period of eight years. He differentiates a form of rheumatism caused by what he terms "thyroid instability," not a true or marked hypothyroidism. It is found in relatively young persons, produces only slight deformities, and usually affects the smaller joints. It seems to progress by fits and starts. In these cases the joint disturbances

are by no means the only trouble. Occasionally there are other signs of thyroid disorder—some evidently attributable to increased thyroid activity, and others (in the majority of cases) caused by a decrease in the thyroid activity.

The manner in which this form of rheumatism responds to treatment varies considerably with the associated manifestations. In the juvenile form, where there is no very serious deformity, the response to treatment is good; and, while the serious, chronic, and so-called "incurable" cases do not respond so rapidly, there is no doubt that persistent thyroid therapy is often decidedly beneficial. The conclusion is that "in many cases of chronic rheumatism thyroid extract is a valuable remedy," which "should be placed in the first rank of the therapeutic armamentarium in the treatment of chronic rheumatism." Lévi recommends a daily dose ranging from 0.05 to 0.3 Gm. (from 1 to 5 gr.) in divided amounts. The average is about 1½ gr. a day, which must be continued for as long as six months. The step-ladder method of dosage mentioned on page 476 is advised.

A more scientific explanation may be found in some interesting experiments by A. Slosse, a past professor of physiology at the University of Brussels. He conducted a number of experiments both in the laboratory and the clinic to connect the disturbances of nitrogenous metabolism with the work of the ductless glands. He concludes from his investigations that under normal circumstances the thyroid secretes a *hormone de désaminisation* (a deaminizing hormone), which influences particularly the nitrogenous exchanges and, when deficient, causes a reduction of the power of the cells throughout the whole organism to split up the albuminoid substances, especially the nucleo-albuminoids from which uric acid and other substances of the purin group are formed. Theoretically, then, the enhancement of thyroid action should aid the nitrogenous metabolism, and a large series of urinalyses made by Slosse and his associates substantiates this hypothesis. The encouraging clinical experiences that have been recorded by a number of writers, especially in France, may be partially explained by these findings.

AN OVARIAN TYPE OF RHEUMATISM—There is another form of chronic rheumatism somewhat similar to that which reacts to thyroid therapy, the principal basis of which is an ovarian insufficiency. This is the rheumatism that appears in women at or shortly after the menopause, and it is quite possible that it is caused largely by thyroid disturbances. At least, it reacts quickly to thyro-ovarian therapy, especially if this measure is applied early in the course of the disease. Paul Dalché, of Paris, reports that ovarian substance has given very good results in such instances, and in practically all cases he combines thyroid with it.

The frequency with which rheumatism may accompany the climacteric has prompted some writers to classify a special type of this disorder as climacteric rheumatism. The difficulty in these cases is based on the upset of the endocrine mechanism responsible for the metabolism and cellular chemistry. Exactly the same thing occurs in climacteric hypertension (45) in connection with the ordinary neurocirculatory upset of this critical age. It is logical that this form of rheumatism should be treated as the climacteric is treated, and that very satisfactory results should follow the use of the indicated pluriglandular therapy supporting the ovarian trinity (80).

ADRENAL CONTROL OF MUSCULAR CHEMISTRY—There is another aspect of chronic muscular rheumatism that has developed in connection with the increasing clinical possibilities of the adrenal cortex hormone. Based on the experience of a correspondent in Oregon, a number of my friends were invited to consider the muscular features of rheumatism from the same point of view as the muscular toxicities of Parkinson's disease (81), cachexia (43), or Addison's disease (35). As a result, Adreno-Cortin* was used empirically in a number of cases. The following excerpt is from the first of a number of encouraging communications, telling of the application of this idea. It happens to be the doctor's own experience:

"While studying your recent literature about the possibilities of the new adrenal cortex hormone, I found something I thought would do some good for my rheumatism. As a result I have been taking Adreno-Cortin, one capsule night and morning. . . . I can say that I have enjoyed more relief than in three years. The pain in my shoulders is nearly all gone. . . ."

This, of course, refers to the muscular features, not to arthritis, which is considered elsewhere (38). The benefit in this and many other similar cases must have been caused by the more efficient muscle detoxication.

The relation of the mineral balance to rheumatism is important. It is probable that part of the initial cause of muscular rheumatism is the gradual stealing away of the body's reserve of alkalies and the development of a condition of acidosis or even uricacidemia, which clogs up the muscular tissue and prevents the normal neutralization of the acid wastes of muscular activity. In addition to attempting to stir up the endocrine activity that presides over these functions, remineralization is a rational associate measure in the treatment of chronic rheumatism (100).

In conclusion let us remember the intimate relation of the ductless glands to metabolism, the undoubted connection between rheumatism and metabolic disturbances, and, therefore, the possibilities of organotherapy as an effective adjunct in the treatment of certain forms of rheumatism.

88. SENILITY

Geriatrics—Premature Senility—"Rejuvenation"—Endocrine Reactivation.

THE ELDERLY patient, no matter what his particular ailment, should always be considered from the endocrine view-point, because the response to the treatment of any disorder depends in a surprising degree upon what might be called "the physiological resilience."

Now, this somewhat intangible factor undoubtedly is dependent upon the endocrines, because the cell chemistry and its response to stimuli, both external and internal, are under the control of the glands of internal secretion.

GERIATRICS—The study of the diseases incident to old age, then, is really a branch of endocrinology; and, as the connection is made clear between senility and the endocrine efficiency or the lack of it, there appear several features of interest from the therapeutist's point of view.

A series of instructive articles on geriatrics by Malford W. Thewlis, of New York, appeared in the *Medical Review of Reviews* during 1923. Senility in its various phases is carefully considered, and the intimate relation of all the endocrine glands is expressed by the statement that

"Old age, with its degenerative changes, causes hypertrophy or atrophy of the ductless glands, with resulting changes in the internal secretions.

"The science of the study of geriatrics is believed to be based upon three fundamental principles: (1) that senility is a physiologic entity like childhood and not a pathologic stage of maturity; (2) that disease in senility is a pathologic condition in a normally degenerating organ or tissue and not a disease such as we find it in maturity, complicated by degeneration; (3) that the object of treatment in senility should be to restore the diseased organ or tissue to the state normal to senility and not a restoration to the condition normal in maturity."

Elsewhere (*Med. Times,* July, 1928, lvi, p. 172), this same author adds:

"As for the endocrine glands, we often find that at the climacteric we are able to do some good with endocrine substances, thereby preventing some conditions which might cause annoying symptoms later. While the symptoms of myxedema are closely related to some of the symptoms of senility, there is no proof that the thyroid gland itself is the cause of premature senility. It would seem that the same factors at play which cause arterial hypertension, arteriosclerosis, and cardiorenal disease, are the very factors which influence the endocrine glands and which produce a condition which we term premature senility. As far as we know, one condition is not the cause or result of the other, but a part of the general picture. In my opinion, many of the symptoms we have attributed to arterial hypertension and arteriosclerosis are actually due to the toxic influences, whatever they are, which cause the arterial conditions, and not to the arterial disease itself."

In no phase of organotherapy have charlatans made so much of their opportunities as in this one, and the insinuations about rejuvenation are just as subtle and just as absurd to-day as they were in the early nineties. Yet it is indeed possible to reactivate depleted functions; and it is proper, when confronted with an endocrine defect, to use every attempt to strengthen the waning cellular activities. But these waning functions are *not* just the sex functions. Herein lies the great misunderstanding about this matter.

PREMATURE SENILITY—There is a great difference between presenility and senility. Premature senility is a real problem that concerns many a man. The strange, abnormally early aging in children, known as progeria (46), is typically an *organic* endocrinopathy. But this is not the presenility that this term indicates.

Premature senility is an abnormally early manifestation of *functional* cellular depletion characterized by the onset of the symptoms of age before they should normally appear. Nine times out of ten the gonads are the endocrines most definitely involved, and more than nine times out of ten the cause is thoughtless, careless stress—the ignoring of the rules of life that moderation and good judgment advise.

The treatment of presenility is not rejuvenation either by organotherapy or by surgery, but the instillation of several doses of common sense with good hygiene, better elimination, and, best of all, physical and mental rest.

Impotence is supposed to be the cardinal symptom of presenility. When it is a real problem, organotherapy calculated to reactivate the entire endocrine mechanism may be added to the general treatment outlined above. Since impotence is a prominent feature of hypogonadism, the treatment is outlined under that heading (58).

"REJUVENATION"—A book on endocrinology would not be complete without reference to the present status of a method that is erroneously called "rejuvenation." The term is unfair, for the suggestion contained in it is impossible. It is quite true that, by certain procedures that will be outlined here, it is possible "to give a man a new lease on life." That, no one will deny. It is also true that the same thing can be done—and for years has been done—by the instillation method referred to above. All will agree that these much-vaunted measures bearing the name of Lydston, Voronoff, Steinach, or Stanley, do indeed accomplish revolutionary changes in many patients, but the improvement is no more spectacular than that to which the endocrinologist is accustomed in a dozen other phases of his work. The point is that so-called rejuvenation does not rejuvenate, if we give this word

its true meaning. Rejuvenation really means "to make young again," and the patient is always older after his treatment than he was before it, even if he feels younger.

In premature senility the physical machinery breaks down before the normal period of involution, usually because it has been overworked. The modern business man, the professional man, and others (even women) go the pace; they "step on it" constantly, and then are surprised that Nature refuses to be a party to their methods. They expect the physician to restore them to full health by giving them something out of a box or a bottle, or by doing "a simple little operation"—possibly during the luncheon hour or between business hours and a golf appointment. Then, presto! they can go on gaily.

But Nature balks. When the body has been overstrained for any length of time, the functions to be lost first are those not essential to life, though necessary to health and contentment. These, in the order of their loss, are the sex functions, the keen mentality, the unlimited power of digestion, and general endurance. All these processes slow up, and the victim feels that he is not so young as he used to be.

All right, let's be rejuvenated. Fatal error! It is the colorful though mistaken imagination of the novelist that popularizes this error. In her vivid novel, "Black Oxen," Gertrude Atherton describes the experiences of an old woman who by some gland treatment was made young again. Such a thing can never be. A woman or a man of sixty can never be renovated according to the pattern and specifications of twenty or thirty. When at sixty these individuals feel and look like eighty, rational treatment in keeping with physiological laws can at best restore them to a fair sixty, but not to less than that. And even then, the treatment involves more than an operation or an X-ray exposure. It literally means making over the whole mechanism, not only physical but mental and emotional. It means retraining all the individual's habits.

The results of rejuvenation by glandular therapy depend of necessity upon the quality and the condition of the patient's organism and upon the manner in which it can react to the substitutive treatment or the homostimulation that is given. An organism that has been ruined by long-continued indulgence cannot possibly be put in as good condition, no matter by what treatment, as one whose possessor has been fairly moderate and is prematurely old merely because he worked too hard.

There is no way by which an exhausted or old roué can be changed back into a virile young buck. The work of the physician is limited by restrictions set by Nature. Ponce de Leon's fountain of youth will never be found, nor

will the philosopher's stone, nor the *Alt' Weiber Brunnen* (the old wives' well). There is nothing mystic or impossible about the proper treatment of old age. It is all very natural. But, at that, the workings of Nature are truly wonderful and marvelous.

ENDOCRINE REACTIVATION—Three methods are suggested for the reactivation of the endocrine function of the gonads. The first is that originally suggested by G. Frank Lydston, of Chicago, who transplanted human testicles into the scrotum. Later, Serge Voronoff, of Paris, continued this work, and published several books and many articles indicating that his procedure, which is essentially a testicular graft, is capable of stimulating to renewed function the gonads as well as other endocrine glands. In a careful consideration of "Rejuvenation: The Endocrine Therapy of the Testis," Kenneth M. Walker, of London (*Practitioner,* July, 1925, cxv, p. 84), reviews the subject in an interesting way. He says:

"In the majority of dystrophies that present themselves for treatment by means of testicular grafts we are not dealing with a lesion confined to the testis, and too much must not be expected of the operation. Even when a case has started as one of pure testicular deficiency, a graft will only confer a certain degree of benefit on account of the reciprocal involvement of other glands and of other structures that has taken place during the lapse of time. The longer the history of the deficiency, the less hopeful is the outlook. An old castrate will not experience so much benefit from a graft as does a subject who has recently suffered testicular loss. It is therefore frequently advisable to combine testicular grafts with the use of extracts of other endocrine glands, notably of the pituitary, the suprarenals, or the thyroid."

When a graft survives, it does not become a permanent part of the patient's body, for atrophy soon begins and is complete in from six to twelve months; rarely can the graft be palpated after eighteen months. The length of time during which a graft survives depends upon several factors, including the vascularization of the graft and freedom from infection. The grafts break down and slough out so often that L. L. Stanley, of San Rafael, California, has made an attempt to avoid this by injecting an emulsion of fresh testicular material into the abdominal wall. His reports from San Quentin prison are quite remarkable. At the meeting of the California State Medical Association (April, 1931) Stanley reported six thousand mass injections of a fresh emulsion of testes, containing a small amount of chloretone, in four thousand patients:

Local reactions were rare, urticaria followed occasionally, 1 per cent. suppurated.

One hundred forty-eight cases of acne were treated, with 99 practically cured in two months.

Twenty-two cases called diabetes were found to be sugar-free after one shot, and in several cases where there was a slight return of the sugar it disappeared after subsequent shots.

Asthmatic attacks are reported to be less severe.

After the injections in 429 run-down cases of postinfluenzal asthenia, etc., there was benefit in 370. The muscle tone was increased and the constipation controlled. The suggestion is that these injections "stepped up" the adrenals, thus causing the improvement.

All the experimental work was originally done on humans and later some of it was checked on animals. One 14-year-old dog, the mascot of the prison, showed remarkable signs of energy, physical and sexual, two days after injection.

Still another method has been discussed quite fully in the literature of the last few years. It is the operation of vasoligation suggested in 1912 by E. Steinach, of Vienna. (Steinach submitted his discoveries to the Academy of Sciences in Vienna in 1912, but it was not until 1920 that he published his work on rejuvenation in *Roux Arch. f. Entwcklngsmechn.,* xlvi.) Steinach's work was based on the discovery of P. Ancel and P. Bouin, of the University of Strasbourg (*Compt. rend. Soc. de biol.,* 1904, lvi, p. 83), who showed in a series of experiments on animals that the ligation of the spermatic duct causes a hypertrophy of the interstitial cells of the testes and an increased functional activity. Steinach duplicated this work in senile rats with quite impressive results, and it has been confirmed repeatedly by David Macht, of Baltimore.

In clinical practice, vasoligature has been done extensively by a number of workers with results that have varied greatly, and it is possible to find the widest differences of opinion in what is already a very large literature.

It seems undoubted that this form of therapy is capable of reactivating endocrine function, but I fully agree with Walker regarding the necessity for attempting to reactivate the other glands as well as the testes, particularly the adrenals and the thyroid.

With all due respect to the surgeons and their expensive operations, I am quite convinced that pluriglandular therapy directed at the gonads themselves and the usually associated glands is capable of accomplishing comparable results. This does not mean that I am comparing my own procedure (58) with the three measures referred to above. I am merely reporting the fact that patients who have received "mass injections" and have been benefited by them have later taken a series of injections of Gonad Co.* and tablets of the corresponding formula with results very similar to those experienced previously. I have also met patients who had submitted to homologous grafts, and who, when the initial improvement began to wane,

were benefited by this same pluriglandular therapy. Lydston himself was one of these, and he repeatedly assured me that oral organotherapy undoubtedly supplemented the beneficial influence of the graft, and, too, that it seemed to prolong its effect (he had three such operations). H. Lyons Hunt routinely supplements the effect of transplantation with a course of pluriglandular organotherapy.

It is of interest in this connection to find that balneologists claim effects that sometimes amount to a reactivation of potency in patients taking mineral baths. In a contribution to *Clinical Medicine* (Nov., 1923, xxx, p. 800), Alfred Martin, of Bad Nauheim, claims such an influence from mineral baths that contain large quantities of calcium chloride. These springs are especially effective for treating cardiac patients, more particularly those with arteriosclerosis. A more direct aphrodisiac action is noted after the administration of carbonic-acid gas baths. It has been observed repeatedly that priapism occurs in poisoning with carbonic-acid gas. Martin quotes an article from the *Revue des deux mondes* for May 15, 1855, as follows:

"There is one peculiarity of the Nauheim baths, both the carbonized brine baths and the gas baths, which should not be passed by silently. The patient may stretch himself out in careless comfort in his carbonated brine bath, the water of which is constantly being renewed and sprayed in large volume and in which the pearls of carbonic acid rise constantly; or he may take a carbonic-acid gas bath—it never fails that he is conscious all over his body of an agreeable titillation and pleasant prickling in the skin which gives rise to sensations that defy the decrepitude of age as well as of premature impotence."

Martin asserts that "rejuvenation" is possible without Steinach's operation if it is remembered that, in Steinach's own definition, "rejuvenation means the relief of troubles incidental to premature and untimely growing old."

Two great errors have interfered with the acceptance by the profession of "rejuvenation." The claims have been too lurid, and the treatment has often been too one-sided. Symptomatic improvement has come about from good hygiene, and the results from the organotherapy have been magnified beyond reason and good judgment. It is possible to make a very considerable difference in a presenile person by a thoroughgoing detoxication and hepatobiliary stimulation (104). When this is supplemented by the pluriglandular therapy already mentioned, the improvement is marked but temporary, for the habits of a lifetime and the actual physical condition of the cells are never changed by any therapy.

89. SPLEEN DISEASE

Malarial Cachexia — Splenomegaly — Chronic Myeloid Leukemia — Eosinophilia.

"THE SPLEEN is the most misunderstood organ in the body." It is hemolytic. It is hemopoietic. It intervenes in the protein metabolism. It controls the utilization of iron. It plays a part in the immunity response. Yet it can be removed with no apparent detriment to the functions that it is supposed to influence. As yet there is no unanimity of opinion as to the rôle that the spleen plays in the bodily economy.

MALARIAL CACHEXIA—The nutritional disorder that results from chronic malaria, known also as paludism, practically always involves the spleen. First, there is a slight enlargement with local tenderness; later, the spleen becomes larger and harder, and splenomegaly develops. Before this chronic stage is reached, spleen extract is used as a preventive of the symptoms and later developments. Given by mouth or by injection, it affords symptomatic benefit in malarial cachexia, but has no effect on the malaria itself. Several Italian writers, however, have claimed that spleen extract renders quinine more potent. Many authors have lauded spleen therapy as a valuable hemopoietic, but within the last few years liver extract has superseded it for this purpose at least.

SPLENOMEGALY—Certain French army physicians interested in organotherapy were transferred from France to the Orient, and before long they became acquainted with pathological conditions of the spleen hardly ever seen in Europe—splenomegaly, chronic splenitis, and malarial spleens. His bent toward the study of organotherapy prompted M. Paucot, among several others, to attempt what was then a new method in the treatment of splenomegaly. In his article published in *Nord médicale* (1907, xxii, p. 53), Paucot told of his experience at Hai-Duong, French Indo-China, with 252 cases of splenomegaly of malarial origin. Of this large series no less than 251 were "cured," that is, the usual symptoms disappeared, and the spleen, which before treatment had measured from 10 to 20 cm. in height, became normal and was neither palpable nor percussible below the ribs. The sole remaining case was benefited in a degree. These results were qualified by a long series of clinical reports from the official government records.

Here is a brief outline of Paucot's procedure: Fresh beef spleens were reduced to a pulp and given in doses of 50 Gm. each morning; 25 Gm. did not give sufficiently rapid results, and more than 50 Gm. seemed to be too

much. An increase in appetite ensued, which later was lost, and a certain repugnance for food developed when the dose was raised much above 50 Gm. Translating directly from the article in question, we read:

"To sum up, this treatment has given me results incomparably superior to those that I have obtained by other methods of treatment. It seems to succeed in every case of chronic splenitis, save only where the spleen has acquired a stone-like hardness and has become adherent to the diaphragm or abdominal wall. Even then, however, there has been amelioration. The general condition is rapidly benefited. The men are so thoroughly cured that they are able to continue their service, thus obviating a considerable expense and loss of men to the Government."

CHRONIC MYELOID LEUKEMIA—The involvement of the spleen in certain leukemias gives the subject some interest from our point of view. Many an effort has been made to apply some of the fundamental principles of endocrinology in the attempt to solve the riddle of the leukemias, but in vain. The limited possibilities in the way of therapy are referred to elsewhere under the heading, "Leukemia" (40).

EOSINOPHILIA—There is a mysterious connection between spleen therapy and eosinophilia. So far, the expressions of opinion about this relationship are few and indefinite. Our present knowledge has come about as a result of clinical experience. Here are some facts that some day will be explained and which already can be utilized with advantage in an empirical way. Eosinophilia, usually expected in conjunction with alimentary infestations, trichinosis, and filariasis, is found in bronchial asthma, certain dermatoses, and urticaria. It has been found that intramuscular injections of spleen solution almost invariably cause a reduction in the eosinophilia. With this change in the blood-count, there may be simultaneous control of the dermatoses and benefit to the asthma. This is empirical treatment but it is being employed more and more with increasing success (50).

90. SURGERY

Adrenalin in Shock—Pituitary in Alimentary Paresis—Insulin in Diabetic Gangrene—Parathyroid in Bone Surgery—Adrenal Support as a Prophylaxis—Presurgical Preparation—Presurgical Liver Hemopoiesis.

"Oh, yes, but you see I do surgery almost exclusively." How many times a statement like this has been made when the subject has been broached in conversation! And yet every surgeon depends upon organotherapy in emergency, and epinephrine and liquor pituitarii are found in every operating-room.

It is in order to outline here the prospects from endocrine therapy in surgical practice.

Adrenalin in Shock—Epinephrine, or adrenalin, is used in shock, hemorrhage, and collapse (45). The usual dose is from 3 to 8 min. intramuscularly. It may also be given intravenously, well diluted in 100 cc. or more of sterile saline solution. For a time, there was quite a furor about the intracardial injection of adrenalin in patients moribund from shock. The local hemostatic effects of adrenalin are too well known to be more than mentioned.

Pituitary in Alimentary Paresis—Pituitrin, or liquor pituitarii, is also used in shock and hypotension, but more often in post-operative ileus, gas pains, and alimentary paresis. The tonic influence of pituitrin on the alimentary muscle is amazing, a small intramuscular dose of, say, 10 international units (18) performing miracles. Many surgeons give a medium-sized dose daily for two or three days before surgery, especially ear, nose, and throat operations. This acts as a prophylactic against hemorrhage.

Insulin in Diabetic Gangrene—Insulin has revolutionized the possibilities of surgery in patients suffering from diabetes mellitus. Under its influence, the heavy mortality from diabetic sepsis has been overcome so that the surgical prognosis is little worse than in non-diabetics.

Of especial interest in this connection is a statement by H. Blotner and R. Fitz, of Boston (*Boston Med. and Surg. Jour.*, June 24, 1926, cxciv, p. 1155):

"We have been particularly interested in the effect of insulin upon the surgical treatment of diabetic gangrene. Up to October, 1922, when insulin was first used in the Hospital [Peter Bent Brigham Hospital], 25 per cent. of the gangrenous cases treated by any method died, while since that date 18 per cent. of the gangrenous cases have died. Insulin, therefore, appears to have had an appreciable effect in lowering the Hospital's mortality-rate of these cases.

"In comparing cases of diabetic gangrene treated surgically with and without insulin, it appears that insulin has afforded a means for rapidly desugarizing patients before operation and for allowing them a liberal diet during the period of convalescence from operation."

A number of papers have been published extolling the outstanding advantages of insulin in surgical practice. For example, Seale Harris, of Birmingham, Alabama (*New Orleans Med. and Surg. Jour.*, Dec., 1924, lxxvii, p. 222), after speaking of insulin as "one of the great epoch-making discoveries of this or any other age," says:

"It has a special bearing in surgery, because, with this new treatment, and with the diabetic patient properly dieted, there is no reason why the diabetic should not be just as good a surgical risk as the man who is not a diabetic."

Later, J. A. Nixon, of Bristol (*Bristol Med.-Chir. Jour.*, 1926, xliii, p. 199), in a paper before the British Medical Association, offered the following conclusions regarding the principal uses of insulin in surgery:

"1. To enable diabetic patients to combat infection either with or without operation.

"2. To render safer for diabetic patients surgical operation whether urgent or deliberate.

"3. To protect diabetic patients against the dangers of anesthesia."

PARATHYROID IN BONE SURGERY—There are some other interesting prophylactic possibilities to which the surgeon's attention is called: As a supplement to alkalinization, or remineralization, parathyroid therapy is now of accepted value; but, in addition to the medical problems, there are several surgical ones that may be mentioned, including bone dystrophies and slowly uniting fractures (41).

In bone tuberculosis, also, the calcium-mordant effect of parathyroid may be used with decided benefit. Again, in this particular class of cases, spleen extract is coming in for renewed attention (94), and a whole new series of prospects are being opened up in the adjuvant treatment of surgical tuberculosis.

There is another possibility from parathyroid therapy. Not only has it arrested hemorrhage from various sources, but it is used successfully to prevent the bleeding of tonsillectomy. I have no doubt that it would be an excellent prophylactic means for making other operations less bloody. Further, it overcomes the tendency to oozing after operation, especially in places where it is difficult to place sutures. B. Gordon and A. Cantarow, of Philadelphia, who used Parathormone, suggest three injections (ten units each), thirty hours apart.

ADRENAL SUPPORT AS A PROPHYLAXIS—Perhaps the most interesting application of pluriglandular therapy in surgical practice is the use of the thyro-adrenal combination—Adreno-Spermin Co.*—which I suggested in 1918 as a means of restoring tone after the depleting experiences that one commonly encounters during anesthesia and following surgery. Two important measures can be used to overcome the expected toxemia and to hasten convalescence:

First, preliminary alkalinization with 100 gr. of sodium bicarbonate a day, with much water, in divided doses for at least three or four days before the operation. This lessens acidosis and builds up an alkali reserve that is available to neutralize the cellular toxemia resulting from the anesthetic and post-operative inactivity.

Secondly, the use of Adreno-Spermin Co. as a general cell tonic. There can be no doubt that the depletion of the surgical patient is identical with that following other forms of toxemia, such as acute infections and alimentary toxemias.

PRESURGICAL PREPARATION—Adrenal support is fundamental in therapeutics. It happens that many a chronic patient whose troubles have led to the necessity for major surgery is in a state of endocrine depletion and toxemia that makes the operative intervention all the more dangerous. The cell-stimulating effect of pluriglandular therapy not only paves the way for better resistance to the jeopardy of an anesthetic but facilitates post-operative convalescence and saves the patient much suffering and discomfort.

Recourse to Adreno-Spermin Co. as a standard preoperative tonic and detoxicant is routine with a number of surgeons. The response to such treatment is really no different from that which we have come to expect from it in true adrenal dysfunction (35), in the depletion of influenza (69) with its postinfluenzal neurocirculatory asthenia, in the run-down states that culminate in neurasthenia (77) or even psychasthenia (71).

The suggestion is to prescribe 100 tablets of Adreno-Spermin Co., half of which are taken prior to the operation 1, q.i.d. or 2, t.i.d., and the other half, 1, t.i.d., starting as soon as possible after the operation.

In many cases the preoperative examination shows that the coagulation time of the blood is greatly delayed. It is not always feasible to depend upon preliminary treatment by means of calcium salts in an attempt to hasten this clotting time or to trust to the influence of hemostatic serum during or after the operation in order to lessen the loss of blood. Since the notable report of the findings of B. Gordon and A. Cantarow (*Jour. Am. Med. Assn.*, April

23, 1927, lxxxviii, p. 1301) on the use of parathyroid extract in hemorrhage, this endocrine remedy has been used as a preoperative measure because it reduces the coagulation time to within normal limits, and apparently prevents hemorrhage.

In those cases in which the patient is seriously anemic, a very simple preoperative measure may be employed, which is a development of the discovery that the liver produces a powerful hemopoietic hormone. Attention is called to this matter in the following paragraphs.

PRESURGICAL LIVER HEMOPOIESIS—In the consideration of the various anemias (40), the value of the hemopoietic liver-nuclein formula known as Heparnucleate* is mentioned in connection with several essentially surgical problems. When a patient requires a gall-bladder operation or some major surgical intervention and the routine preliminary blood-count shows that a general anesthetic should not be given, it is gratifying to be able to expect an increase of a million red cells from such treatment in ten days or two weeks.

Liver therapy has served so well in preparing anemic patients for surgery that the risks have been noticeably reduced. The general improvement has been so uniform and dependable that many a surgeon now prescribes 12 vials of Heparnucleate during the six days before the expected operation, regardless of the blood-count.

91. SYMPATHICOTONIA AND VAGOTONIA

THE AUTONOMIC or vegetative nervous system has a very close relationship with the endocrine system. There is evidence to show that the sympathetic is stimulated by certain of the glands of internal secretion, and at the same time the sympathetic stimulates them reciprocally.

The vegetative nervous system, as it is sometimes called, consists of two fairly distinct anatomic divisions which more or less balance each other, *viz.*, the sympathetic (the thoracolumbar division) and the parasympathetic (the vagus, or craniobulbosacral division).

In the introduction to his excellent book, "Symptoms of Visceral Disease" (St. Louis, C. V. Mosby Company, 1919, p. 26), F. M. Pottenger, of Los Angeles, says:

"The vegetative nervous system, being that system which cares for those functions without which the animal cannot exist, is given the chief, if not the entire, control of metabolic activity. The reason for the doubt in this statement is the uncertainty whether or not we must consider that some of the glands of internal secretion are in part without nerve control; and also because, as yet, we cannot assert that all internal secretions act on or through the nerves, because their action has not thus far been thoroughly proved. Nevertheless, we are within the bounds of known facts when we assert that the adult human being expresses most of his physiologic activity through nerves, and that his normal metabolic activity, for the most part at least, is under the control of the vegetative nervous system. Therefore the study of the physiologic activity of his vegetative nervous system becomes a duty of clinicians. Its pathologic activity expresses itself in disturbed function and is the most important bridge between pathologic stimuli and the pathologic changes in tissues, secretions, and excretions. The vegetative nervous system then, when its normal action is disturbed, is the chief cause of the symptoms of visceral disease. It affords the common bridge between activator and end-result."

The interest of the profession in the functional relationship of the sympathetic system to the endocrines is based largely on the hypothesis of Hans Eppinger and Leo Hess, of Vienna, to whom we are indebted for an explanation of the clinical pictures of sympathicotonia and vagotonia. The following are the main features of their hypothesis:

1. Based on pharmacological rather than anatomical grounds, a complete antagonism is assumed between the parasympathetic and sympathetic systems.

2. The chromaffin system is closely allied to the sympathetic system; and adrenalin, which produces effects similar to those resulting from experimental stimulation of the sympathetic, has no direct action on the parasympathetic.

3. The existence of a hormone that acts on the parasympathetic is assumed. This has been called "autonomin," and it is suggested that it may exist in the pancreas. Possibly it is akin to the circulatory hormone of the pancreas developed since 1929 (15). There is no proof that this hormone actually exists, although a non-pressor extract from the adrenal cortex acts as a stimulant to the parasympathetic.

4. Since autonomin is still a hypothetical principle, certain drugs known to have an action on the parasympathetic system are utilized. Pilocarpine, picrotoxin, muscarine, and physostigmine have a stimulating action. Atropine has a paralyzing action. None of these drugs has a universal action. By their use Eppinger and Hess attempt to identify a distinct group of patients who show an abnormal sensitiveness to pilocarpine and an abnormal insensitiveness to atropine, regarding this as evidence of a state of vagotonia. As those who are especially sensitive to adrenalin are relatively tolerant to pilocarpine, and vice versa, they argue that there must be a pharmacodynamic antagonism between these two substances. It cannot be overlooked, however, that some persons are sensitive to both pilocarpine and adrenalin, and others are frequently encountered who exhibit an idiosyncrasy to drugs that act upon all the autonomics. Also, it must be admitted that there are many conditions, normal and abnormal, in which both of these systems are brought into activity simultaneously.

Without the help of the glands of internal secretion the vegetative system probably could not function—at least, not purposefully or regularly and conservatively. Walter Timme, of New York ("Nelson Loose-Leaf Living Medicine," New York, Thomas Nelson & Sons, 1920, Vol. VI, p. 637), says of this:

"Together, the sympathetic nervous system and these glandular elements form a basic physiologic whole of great complexity of arrangements, of interrelativity of action, of coordinated purposeful activity, which maintains the continuity of the vital functions, controls the metabolic activity of the entire organism, including probably growth, repair, and removal of the products of oxidation of its cellular elements, and combines with the other nervous domains, the sensorimotor and psychic, to unify and fix the individual. . . .The coordination and interrelation among the several spheres—vegetative, sensorimotor, and psychic—is so close, that no disturbance in any one can take place without some concomitant change of state occurring in the other two. It can readily be seen, therefore, that the sympathetic nervous system with its internal glandular mechanism must play subsidiary, though important, rôles in diseases of the psychic and sensorimotor domain, while, in a host of disturbances heretofore classified as functional or unclassified or classified incorrectly, this system through its disturbance plays the chief part. . . . no diagnosis can be complete without assigning to the sympathetic nervous

system and the internal glandular mechanism their proper rôle in such diagnosis."

Every student of endocrinology recognizes two great classes of functional endocrine imbalance—the hyperfunctioning and the hypofunctioning. Where there is a functional excess of the predominating endocrines, usually there is sympathetic irritability; and, on the contrary, vagotonia, or parasympathetic irritability, is seen in conditions that overrule the sympathetic-stimulating endocrine mechanism.

The consensus at present seems to be that the vagotonia and sympathicotonia visualized by Eppinger and Hess rest more upon a theoretical than a practical basis. Moreover, a little thought must convince one that a person cannot be wholly vagotonic or sympathicotonic and survive. Consequently, complete vagotonia or complete sympathicotonia is never seen. A patient and his disturbance can be classified only as to which group of symptoms predominate. Practically all known diseases have a predilection to produce one or the other of these pictures in varying degree.

Hence the terms "vagotonia" and "sympathicotonia" denote, not disease processes, but symptom groups that may arise in any disease and may be seen to some extent in most people. A tendency one way or the other is part of the physiological substratum and the temperament, and is inseparable from the individual. A man is sick with vagotonia or sympathicotonia only when one or the other symptom-complex markedly predominates to his genuine discomfort.

The symptoms of sympathicotonia are fairly constant, though it is difficult to give each one in its exact endocrine connection and value. The following symptoms may be constant or may manifest themselves only under special conditions:

1. The patients are high-strung and impulsive, and have what George Bernard Shaw aptly calls "chronic hyperesthesia."

2. The eyes often are bright and prominent and the pupils large.

3. Many sympathicotonic persons suggest by their appearance a picture of the hyperthyroid patient (63). In these individuals there exists a mutual and reversible influence between the function of the thyroid gland and that of the nervous system, forming a vicious circle; in other words, there is a mutual abnormal reactivity. (Thyroid hyperactivity puts the nervous system into a state of evident hyperirritability which, in turn, influences the entire organism and keeps the thyroid in a constant state of overactivity.) There is reason to believe that similar relations exist between the autonomic system and the glands of internal secretion.

4. The most constant feature of this syndrome is cardiovascular irritability manifested as throbbings over the precordial area and in the head, and palpitations occurring during fatigue or severe emotion. Infectious diseases, even when apparently not at all severe, give rise to maximum degrees of tachycardia.

5. Practically all neuropaths and psychopaths manifest evidences of a very unstable sympathetic system.

6. There are other symptoms such as a noticeably warm, dry skin, and a tendency to gastric disorders due to deficient acid.

7. Epinephrine, posterior pituitary, and thyroid extracts aggravate all these symptoms.

To my way of thinking, these persons have an endocrine mechanism that for a long time has been slightly and subtly overstimulated. Temperamentally and from an endocrine standpoint, they are of the hair-trigger variety. A minor stimulus goes a long way, little troubles loom large to them, a comparatively small effort empties the reserve tank; and a slight illness affects them far more than it does the opposite type.

On the other hand, vagotonia is a hyperexcitability of the parasympathetic or vagus system. This usually is found in youthful or middle-aged persons who exhibit a train of symptoms quite different from those outlined above, namely:

1. The pupils are contracted, and the palpebral fissures narrow.

2. Gastric hyperacidity is common, with a tendency to referred pain. There is increased peristalsis, and diarrhea may occur on excitement, though spastic constipation is frequent, with small stools sometimes associated with mucus.

3. There is a feeling of inability to expire and a sensation of pressure on the chest, with a general tendency to apprehension and anxiety.

4. The pulse is quite consistently slow. Vasomotor angina is found, and a condition of pseudo-heart-block may develop.

5. The vagotonic also has hyposphyxia (45) with a low blood-pressure; cool, pale skin that perspires easily; and typical clammy hands and feet.

6. There is a tendency to increased sugar tolerance.

7. There is sensitiveness to proteins and to pilocarpine, with urticaria, asthma, and eosinophilia. Dermographia is frequent.

8. In males, erethism, frequent erections, early ejaculation, and nocturnal emissions are usual; in females, a tendency to virilism is recorded.

9. Seasickness and car sickness have been considered as vagotonic manifestations. These may be controlled occasionally by atropine.

The irritability usually diminishes with advancing years, and the vagotonia improves correspondingly.

But what clinical help do we get from these data? Is there a treatment for sympathicotonia or its antithesis? It is regrettable that the answer must be "No." It is an inherent, inherited status, like the features or the build; it is a physiological attitude—and one cannot change such ingrown cellular leanings.

But the physician who differentiates these types also has learned that the sympathicotonic patient does not need more stimulation. Hence strychnine, coffee, and poisons are contraindicated—fundamentally, not necessarily individually. These cases need sedation—in their living, their amusements, and their treatment.

The vagotonic needs alkalies, endocrine stimulation, detoxication. The vagus is irritated in chronic liver defects, and the picture of hypohepatism (66) has many points in common with vagotonia.

An illuminating clinical paper on the relation of the vegetative nervous system to clinical problems was published ten years ago by W. V. P. Garretson, of New York (*New York Med. Jour.*, July 6, 1921, cxiv, p. 35). A part of it, bearing particularly upon its relation to dysmenorrhea, is quoted in Chapter 80.

Finally, a quotation from "A Text-Book of Clinical Neurology," by I. S. Wechsler, of New York (Philadelphia, W. B. Saunders Company, 1927, p. 617):

"All the facts thus far accumulated point to a reciprocal relationship between the glands of internal secretions and both the vegetative and the cerebrospinal nervous systems. . . . The intimacy of the relationship is attested morphologically, anatomically, physiologically, pharmacologically, and clinically."

Fascinating, salutary, and useful may be the eventual demonstration of the details of this complex "reciprocal relationship."

92. SYPHILIS

Syphilitic Endocrine Disease—Pituitary Gumma—Endocrine Therapy in Syphilis—The Benefits of Iodine.

THIS PROTEAN specific disease is of peculiar endocrine interest, for the infection itself can directly involve any of the ductless glands, and the systemic toxemia produced thereby exerts a subtle influence on the endocrines. Further, the congenital manifestations of hereditary syphilis often show themselves as endocrinopathies. So often does the defective child suffer from congenital lues, that syphilis must always be considered, whatever the type or degree of the defect.

What can be done for the syphilitic from the endocrine standpoint? Many things: but all treatment must depend upon the patient's history and the evidences of dyscrinism that it reveals.

Sometimes the endocrine features of syphilis are not clear and decisive. The first suggestion to consider this aspect of a given case may come from the failure of the patient to respond to antisyphilitic therapy. There is enough clinical evidence available to allow the claim that the arousing of dormant endocrine functions is doubly justifiable when it is clear that the organism is "at the last gasp" in its fight against disease. Immunity, detoxication, and nutrition are definitely dependent upon endocrine efficacy.

SYPHILITIC ENDOCRINE DISEASE—Syphilis attacks all the endocrines, but some are more liable to be affected than others. In fifteen hundred syphilitic cases brought to autopsy at the University of Michigan, A. S. Warthin (1928) found lesions of the liver, pancreas, adrenals, spleen, and testicles. Previously (1923), W. H. Brown and L. Pearce, of the Rockefeller Institute, in experiments with luetic rabbits, found distinct changes in the appearance and structure of the thyroid, parathyroids, thymus, adrenals, pituitary, liver, and spleen—more especially of the first three. It is noteworthy that even after the disease was controlled these changes were more or less permanent.

The testes are especially susceptible to injury from syphilis. Besides the disturbances in the function of spermatogenesis caused by syphilitic orchitis, there may be an alteration in the internal secretion of the testes. It is even possible that eunuchoidism (58) may be due to inherited lues.

The thyroid is more often affected than infected, *i.e.*, the gland suffers from the stress put upon it rather than from an actual syphilitic process in the gland itself. But a specific chronic inflammatory process may occur in the thyroid gland, which is accompanied by the development of a fibroid goitre with thyroid irritability in the early stages and with an ultimate maximum

degree of hypothyroidism. In such conditions, antiluetic treatment is more effective than any of the accepted endocrine measures. There is good authority for the belief, however, that both hypothyroidism and hyperthyroidism are occasionally caused by syphilis. C. E. Henry, of Minneapolis, also E. Hertoghe, of Antwerp, blame syphilis for many cases of hypothyroidism; while other authors (for instance, E. Schulmann, of Paris) have found that exophthalmic goitre is attributable to syphilis in a large percentage of cases. According to Henry (*Am. Jour. Syphilis,* July, 1928, xii, p. 322),

"It is more probable that a patient with a simple goitre who acquires syphilis will develop toxic goitre symptoms, the burden of the increased toxemia thrown on the thyroid being enough to change the nature of the goitre."

PITUITARY GUMMA—Pituitary disease of a functional nature, or pituitary tumor, with its pressure symptoms and adiposogenital dystrophy, is frequently found to be of syphilitic origin. Surprising as this may seem, it is an advantage, for antisyphilitic therapy is likely to be more satisfactory than the treatment of pituitary tumor of non-specific origin. Several observers have affirmed that acromegaly is caused by syphilis. C. D. Camp, of Ann Arbor (1926), reports an involvement of the pituitary in a case of syphilitic epilepsy. The patient had to be treated with both pituitary extract and antisyphilitic remedies.

Diabetes insipidus may be of specific origin. Warthin has observed that an interstitial pancreatitis leading to atrophy and fibrosis of the pancreas occurs in both men and women with latent syphilis; but, according to Fanoy, there is a comparative rarity of diabetes mellitus in the subjects of hereditary syphilis, despite the frequency of syphilitic lesions of the pancreas. This is explained by the increase in the islands of Langerhans caused by the defensive reaction.

As to the effect of syphilis on the ovaries, it is interesting to note that Warthin, who studied this subject in so many autopsies, has never seen a gumma of the ovary or any other lesion characteristic of syphilis. On the other hand, J. Récamier, of Paris (1926), in treating twenty-one women and girls suffering from congenital syphilis, found indisputable evidence of ovarian derangement—but it was evidently functional and dependent upon dyscrinism elsewhere.

The adrenals suffer perceptibly from syphilis. The asthenia and depletion so commonly noticed are usually adrenal in origin, and this phase should always be treated by means of adrenal support. Warthin noted small foci of lymphocyte and plasma-cell infiltration in both the medulla and the cortex

of the adrenals in the majority of latent syphilitics, male and female, these findings being particularly marked in the female. Even Addison's disease may be due to syphilis, but this is probably the rarest cause—the most common one is tuberculosis.

ENDOCRINE THERAPY IN SYPHILIS—From the foregoing it is apparent that, although the treatment of syphilis has nothing to do with the endocrines, it is manifestly wrong, when the endocrines are involved, to treat the infection and leave the endocrine regulation to nature.

Since the toxemia of chronic tertiary syphilis acts on the glands of internal secretion as does any other serious toxemia, the treatment of the luetic patient should include more than antisyphilitic remedies. These latter are really a form of skilful poisoning—enough to destroy the *Treponema* but not enough to damage the structures of the body. Obviously, the actual antisyphilitic treatment itself is hard on the endocrines.

Many workers have reported very satisfactory results with organotherapy as an adjunct to antisyphilitic treatment. J. Nicolas and J. Cate, of Lyons, France (1926), believe that there is a group of uniglandular and pluriglandular syndromes ascribable to congenital syphilis, and that it is consistent to combine organotherapeutic treatment with antisyphilitic measures. The same view is held by André Léri and R. Barthélemy, of Paris.

In treating women and girls with congenital syphilis, Récamier considers organotherapy as an indispensable adjuvant to the regular treatment of syphilis. Also, in the previously-mentioned case of pituitary involvement in syphilitic epilepsy reported by Camp, the combination of pituitary extract and antisyphilitic remedies brought successful results.

THE BENEFITS OF IODINE—The opinion has been advanced that the iodides are especially valuable in syphilitic dyscrinism because of the iodine effects upon and through the thyroid gland. Schulmann (1920) advises suitable organotherapy combined with potassium iodide whenever there is a possibility that syphilis is responsible for the endocrine derangement, and he says that the syphilitic cause of endocrine dysfunction is far more common than is generally realized. While the present trend of antisyphilitic therapy is away from the iodides and mercury, and, although bismuth is now taking first place, it is still worth bearing in mind that iodine is a valuable endocrine regulator. This may account for some of the encouraging reports about bismuth-quinine-iodide (Tartro-Quiniobine) in the resistant, Wassermann-fast cases of syphilis.

93. THYMUS DISORDERS

Status Thymicolymphaticus—Timme's Syndrome—Many Wrong Diagnoses—More Than a Thymus Dystrophy—Outline of Treatment.

IN OUR consideration of the physiological aspects of the thymus (23) we have learned that it is an oddity about which misunderstanding and controversy are still rife. Apparently the same is true with regard to its clinical and pathological aspects. So great has been this misunderstanding that the British Medical Research Council has recently sponsored a committee to investigate the subject of the thymus in relation to its most commonly observed syndrome. Inasmuch as we are asked to revise our opinions radically, let us recall the essentials of the previously accepted position.

STATUS THYMICOLYMPHATICUS—More than three hundred years ago, Felix Plater, of Basel, described the condition now known as thymus death, the so-called *Thymustod* or *mors thymica*—sudden death of a child for no apparent reason but with an enlarged thymus found at autopsy. This condition was described more exactly in 1889 by several Viennese workers—Klose, Matti, and Paltauf—who named it *status lymphaticus.* (It is now more frequently called *status thymicolymphaticus.*) They called it a specific constitutional disorder of infants and children in which two points are predominant: (1) lymphatic hyperplasia including an enlarged thymus and a marked increase in the amount of lymphatic tissue—adenoids, tonsils, lymph glands in various locations, etc.—and (2) a peculiarly decreased resistance to toxemia (from serum protein or anesthesia, for instance) and to certain more or less insignificant external impressions that result in unconsciousness, convulsions, and sudden death. Usually this syndrome is first found at the death-bed or autopsy table. In fact, so frequently has this been the case that concerted efforts are being made to forestall the dire outcome by thorough diagnostic investigation of all "lymphatic" infants.

A. Stanley Kirkland, of St. John, N. B. (*Can. Med. Assn. Jour.,* Nov., 1930, xxiii, p. 661), divides all children with thymic symptoms into three age groups: (1) Those who have difficulty in the first few hours of life; (2) those whose difficulty appears in the first weeks of life; and (3) those whose persistently enlarged thymuses endanger their lives until puberty or even later. Kirkland's description of the clinical picture of the second group is that of the infant who has difficulty in feeding associated with some cyanosis and dyspnea, who chokes when crying, and may have a crow or inspiratory stridor. Usually X-ray examination shows an enlarged upper mediastinal shadow, which Roentgenotherapy ordinarily restores to normal. But an

X-ray demonstration of a large thymic shadow is only part of the clinical picture, and is not essential for a diagnosis. In cases where there is a shadow it may remain exactly the same size after X-ray treatment, although in the meantime the symptoms may have been relieved by the irradiation. Apparently, then, the alarming symptoms ascribed to thymic dysfunction may have nothing definite to do with the thymus gland.

The size of the upper air-passages in these hypoplastic children may be so small that noisy breathing results, especially when the already limited postpharyngeal space is lessened by adenoids. Sometimes this is mistaken for thymic stridor or asthma (39), and the diagnosis may be confusing because of the fact that the thymus is enlarged. Another diagnostic point is the high-arched palate which, however, may vary as the development changes.

Not all these lymphatic children die in infancy. In fact, an astonishing number are in the third class mentioned above. As they grow older it is seen that they develop differently, have a somewhat unusual appearance, and fall into a category known as *status hypoplasticus*.

TIMME'S SYNDROME—It was left to Walter Timme, the New York neuro-endocrinologist, to explain these more advanced cases of thymus disorder. He postulates a thymus-pituitary-adrenal syndrome, which bears his name. Here is Timme's own picture (Cecil's "Text-Book of Medicine," Philadelphia, W. B. Saunders Company, 1930, p. 1193):

There is "marked lack of differentiation during development. The children mature very slowly, and secondary sex characteristics are late in appearing. The epiphyses remain ununited, and growth is disproportionate, the arms and legs being too long for the trunk. The developmental abnormalities range from almost complete infantilism to the presence of a maxillary torus in an otherwise structurally perfect individual. Failure of differentiation is not confined to the structure, but includes physiology, chemistry, and mental and behavioristic fields as well. Physiologically, patients tend to the *habitus asthenicus* type, with low blood-pressure, flabby musculature, and lack of resistance to fatigue and infection. Chemically they are predisposed to low blood sugar, acidosis, and prolonged coagulation time of the blood. There is usually a relative lymphocytosis. In respect to behavior they remain children. They follow the path of least resistance, shirk responsibility, and lack ability to concentrate. Consequently, they are apt to feel inadequate and inferior."

MANY WRONG DIAGNOSES—But a new note is being sounded in the literature on thymus disorders. For example, according to Roger L. J. Kennedy and Gordon B. New, of Rochester, Minnesota (*Jour. Am. Med. Assn.*, April 18, 1931, xcvi, p. 1286), a diagnosis of enlarged thymus is frequently made in cases in which further examination discloses other condi-

tions as the cause of the symptoms. Stridor, dyspnea, hoarseness, spells of cyanosis, and wheezy or noisy respiration usually can be accounted for on other bases than that of enlarged thymus. Laryngoscopic examination is often necessary for a definite diagnosis. Kennedy and New express the opinion that enlargement of the thymus can seldom, if ever, be established as a cause of death. Preoperative examination and care of infants and children should aim to find and correct all conditions that would make the surgical risk any greater.

Prior to the publication of the foregoing opinions, E. Moro, of Heidelberg (*Klin. Wchnschr.*, Nov. 22, 1930, ix, p. 2185), had drawn his conclusions that congenital hyperplasia of the thymus has nothing to do with the so-called *status thymicolymphaticus,* which describes the lymphatic type of fat and flabby children with an exudative diathesis. They have hyperplasia of the whole lymphatic apparatus of the body, and the enlarged thymus is a part of the clinical picture. The liability to sudden death, however, is not a feature of this condition. On the other hand, says Moro, the sudden failure of the heart is the central point of the whole thymus problem; and a better term for the condition would be *status cardiothymicus,* which he believes to be a definite pathological entity. He discusses the possible connection between the thymic enlargement and the cardiac failure, mentioning as etiological possibilities such conditions as hyperthymization, dysthymization, hormonal dysharmony, and an anatomical, nervous theory.

In Great Britain the impression has been growing that *status thymicolymphaticus* is not the cause of many of the sudden deaths that have been attributed to it. The Medical Research Council, with the cooperation of the Pathological Society of Great Britain and Ireland (*Brit. Med. Jour.*, March, 14, 1931, i, p. 468), has instigated a series of meticulous investigations into 680 deaths under this category that came to the attention of coroners. In an editorial discussion of this in the *Journal of the American Medical Association* (May 23, 1931, xcvi, p. 1797) appears the following:

"They were unable to find any constant enlargement of the thymus in deaths in which the cause was not adequately explained. A constant relationship between the weight of the thymus and the lymphatic tissue was not found. The average weight of the thymus was above normal in subjects with exophthalmic goitre. The arterial hypoplasia that has been described in association with an abnormally large thymus was not demonstrated in this series. They conclude that there is 'no evidence that the so-called *status thymicolymphaticus* has any existence as a pathological entity.' J. A. Hammar, M. Greenwood, and H. M. Woods (*Jour. Hyg.*, Aug., 1927, xxvi, p. 305) have drawn similar conclusions in recent articles. Edith Boyd ("Growth of the Thymus," *Am. Jour. Dis. Child.*, June, 1927, xxxiii, p. 867) declares that

the anatomic picture described by Paltauf 'represents the normal thymus and lymphatic tissue of the well-nourished child.' David Marine ("Status Lymphaticus," *Arch. Path.*, April, 1928, v, p. 661), however, in his recent review of the subject, criticizes the work of Greenwood and Woods, declaring that they considered only the thymus, which is not always enlarged in *status lymphaticus*. Yet he admits that the size of the thymus and lymphatic tissue represents the lymphoid reaction of the individual at any time and that the thymus and lymphatic tissue may or may not be enlarged at the time of death in *status lymphaticus*. One must conclude, then, that if *status lymphaticus* does exist there are no known pathologic characteristics which are distinctive. The special liability to death remains as the one undisputed characteristic on which the diagnosis of *status lymphaticus* has been made."

MORE THAN A THYMUS DYSTROPHY—While opinion on the subject settles, it may be suggested (1) that there is no norm of thymus size or function and that these features differ decidedly in different infants; (2) that unknown factors in the chemistry of the thymus tissue, presumably of a hormone nature but not necessarily associated with structural changes in the cells, cause a series of reactions elsewhere which lead to the two outstanding features of *status thymicolymphaticus* already mentioned; (3) that these hormone influences are not necessarily proportionate to the amount of thymus tissue present; (4) that the undoubted benefit from X-ray therapy to a presumably enlarged thymus alters the hormone balance in such a way that there is control of the factors that make these children susceptible; (5) that thymus death is a result of a syndrome including much more than the thymus picture previously connected therewith; and (6) that the British report indicates that there has been laxity in the reports of the causes of death rather than that the thymus is not functionally connected with this syndrome.

OUTLINE OF TREATMENT—Timme evidently has given more thought to the treatment of *status thymicolymphaticus* than any other writer in this country. His explanation of the endocrine reactions (23) lays the foundation for supportive endocrine therapy. The following recommendations for the treatment of Timme's triglandular compensatory syndrome apply in practically all thymus cases:

1. Deep X-ray therapy to the thymus area.
2. Sodium iodide, gr. 1 to 5 daily, depending upon the age of the child.
3. Because the pituitary seems to be an especially important part of the compensatory mechanism, pituitary therapy with whole gland and anterior lobe is given by mouth and hypodermically to tolerance. Timme adds a comment that fits in with my own pluriglandular predilections (*loc. cit.*, p. 1194):

"Pituitary is more efficacious if combined with small amounts of sodium iodide and occasionally with small doses of thyroid (gr. 1/10 to 1/2 daily)."

94. TUBERCULOSIS

Dyscrinism in the Tuberculous—Spleen Therapy in Tuberculosis—The Regulation of Lime in the Tissues—Lime Starvation and Colloidogenesis—The Adrenals as Fatigue Factors—The Defenses against Tuberculosis—The Importance of Dysovarism—Tuberculosis and the Pancreas.

"TUBERCULOSIS AN endocrine problem? Absurd. Every one knows that tuberculosis is an infection. . . ." There was more to this arraignment of the idea that the glands of internal secretion could have any bearing whatever on tuberculosis. This position, quite in line with that taken by several leading authorities, is based on the conclusion that tuberculosis causes the customary picture of malnutrition, lowered resistance, and subnormal function, rather than the opposite.

Now none can deny the reality of the connection between an active lung infection and loss in weight and the run-down condition, for statistics prove it beyond a doubt. But these statistics do not prove which came first—the infection or the depletion. This question is quite akin to the proverbial one about the egg and the hen. The answer must be taken by faith.

DYSCRINISM IN THE TUBERCULOUS—I submit here the thesis that *tuberculosis virtually always is also an endocrine problem,* and hope to confirm this position to the satisfaction of every reasonable-minded reader. Then, if this is accomplished, it will be proper to suggest the addition of something to the customary antituberculosis routine to care for the dyscrinism also.

First let us consider some fundamentals, oft-repeated but still true:

1. Nutrition—assimilation, detoxication, and elimination—is under the control of the glands of internal secretion.

2. Resistance, while less obviously regulated by the endocrines, is dependent upon the nutrition, circulation, and cellular chemistry.

3. The chemistry of calcium is an important part of the defense mechanism of the body, and "lime starvation" is as usual a finding in the tuberculous as is the *Bacillus tuberculosis* itself. Further, lime is a vital factor in the reaction of the organism to bacterial invasion, just as it is in the calcification of a tuberculous area in the lung. The capacity of the organism to utilize lime is directly under endocrine control.

4. Least tangible of all is the fact that the harmony of the body functions of the tuberculous patient is sorely upset—not only the all-essential functions already referred to, but the sympathetic tone, the point of view, the appetite, and the capacity to cope with what in other circumstances are merely inci-

dental matters. Beyond question, the hormones are responsible for bodily harmony.

In tuberculosis, the physician has a problem to solve which requires the application of every fact bearing upon it. The patient himself has a fight to make in which he needs every resource that can possibly be mustered. While it is planned to enlarge upon some facts and resources that are at our disposal, it is not intended to minimize any one of the available measures already used in the prophylaxis and treatment of tuberculosis.

Whether as cause or effect, dyscrinism is always present in the tuberculous. There is good reason to believe that the reduced resistance that allows the ever-present tubercle bacilli to get a firm hold is essentially a result of a defect in which the endocrines play a part. Then, after the disease is established, the toxemia and nutritional imbalance that accompany the infection are responsible for at least two forms of dyscrinism—*hypoadrenia* with its asthenia and hyposphyxia, and *hypocalcemia* with its lime starvation and upset mineral balance. These two subjects have aroused much discussion and research, but the prospect as I outlined it several years ago remains as potential to-day as ever.

SPLEEN THERAPY IN TUBERCULOSIS—The best way to bring this subject to the reader's attention is to relate a personal incident just as it happened. It is a human-interest story with some conclusions which, I believe, open further possibilities in the treatment of tuberculosis.

In 1912, a fortunate combination of circumstances brought me in contact with the late Sir Lauder Brunton, a leading London internist and, at that time, chief of the medical staff of St. Bartholomew's Hospital. Sir Lauder knew of my interest in the internal secretions and kindly invited me to visit him at his home on Stratford Place. Our conversation drifted toward the possibility of the spleen's being an organ of internal secretion, and what part it might play in the defenses of the body.

The upshot of my visit was that, at Sir Lauder's request, I prepared an article entitled "The Therapeutic Action of Spleen Extract and Its Application in the Treatment of Tuberculosis," which so pleased him that he sent it with a word of comment to the editor of the *Lancet,* and it eventually appeared in that periodical (1913, i, p. 524).

This article came to the attention of Dr. T. N. Kelynack, for many years editor of the *British Journal of Tuberculosis,* who asked me to prepare a paper for his journal. This contribution was entitled "The Adjunct Treatment of Tuberculosis with Certain Organic Extracts," and was also published in 1913.

It is fitting to recall some of the impressions received from the earlier use of spleen therapy in tuberculosis. I have gained much interest in the subject from my correspondence with Dr. Charles Bayle, of Cannes, France. His theory was first brought before the profession at the International Congress of Tuberculosis, in Rome, in April, 1912, at which, among other things, he said:

"I feel authorized by my results to call splenic opotherapy a specific treatment for tuberculosis. It is specific from the therapeutic view-point, because it modifies the soil, rendering it less suitable as a medium for the growth of the bacillus of Koch. It is specific from the practical view-point, because it manifests all the function and rapidity of action of a specific medication. Employed in convalescents, it prevents tuberculosis by increasing the mineral content of the tissue (*en réminéralisant le terrain*). Employed in confirmed cases of tuberculosis, it cures them."

Previous to this, Bayle had written another article in which he referred to 150 patients that he had treated in this manner, 146 of whom "showed the unquestionable and rapid effects of the treatment." He continues (*Tr. Internat. Tuberc. Cong.*, Rome, 1912):

"Among those cases that I have been able to follow for a length of time sufficient to arrive at a conclusion, I note clinical cure in 75 per cent. (the author used the word *guérison*—cure), some of which had been in a very advanced stage and regarding which I had no hope to begin with."

Not every one who has applied spleen therapy in tuberculosis has obtained such results, but the prospect is still interesting, to say the least.

During the last ten years there have been a number of reports accentuating the value of spleen therapy in tuberculosis. For example, in the *Canadian Medical Association Journal* (Jan., 1930, xxii, p. 31), G. F. Watson, of Kitchener, Ontario, reports that spleen therapy has been "decidedly encouraging" in tuberculosis. In the same journal (*ibid.*, p. 33), W. D. Swan, of Hamilton, Ontario, observes that

". . . from the results I have obtained in the treatment of tuberculosis with spleen extract, I would conclude that it has a specific effect on this disease."

Prior to this, several French and German workers had expressed themselves in favor of spleen therapy. P. Ruttgers and A. Kamsler (*Beitr. z. Klin. d. Tuberk.*, 1929, lxxii, p. 1; *ibid.*, p. 68) reported excellent results with spleen diet in several cases of tuberculosis in which other forms of treatment had been unsuccessful.

One of the most interesting of the recent French reports is that of P.-F. Armand-Delille, of Paris (*Rev. de la tuberc.*, April, 1928, ix, p. 256), who started to treat pulmonary tuberculosis in children either by

irradiation of the spleen or by subcutaneous injection of spleen extract. Quoting from an abstract of this article in *American Medicine* (Aug., 1928, xxxiv, p. 524):

"Profoundly skeptical of this theory, yet feeling that it is the physician's duty to neglect no possible method of treatment where no specific remedy is available, the author, over a period of two years, treated a number of children suffering from pulmonary tuberculosis with a filtrate of glycerin splenic emulsion prepared according to the method of Bayle, of Cannes. Although the author tried this treatment only in cases which he considered hopeless and in which pneumothorax was not possible because of adhesions or because the bilateral lesions appeared too serious or too diffuse to risk double collapse therapy, he noted to his great surprise considerable improvement in a number of cases. Fully aware of the fact that even in advanced cases of pulmonary tuberculosis, improvement may occur even without treatment, and although in some cases the injections of splenic extract remained inefficacious, Armand-Delille is convinced that the results obtained are more than fortunate coincidence and that the subject is worthy of further study."

Otto Fliegel, of Vienna (*Med. Press,* Jan. 9, 1929, cxxvii, p. 39), believes that spleen therapy has a direct effect on the bacteria-destroying powers of the body. His experience was largely with tuberculosis of the joints, and his therapy was really a form of dietetics, for he used 5, or at most, 10 cg. of calves' spleen daily, lightly fried or minced in soup, for from two to four weeks. The results are outlined in an abstract of this article in the *Journal of Organotherapy* (July-Aug., 1929, xiii, p. 221):

"(1) A fall in the temperature previously recorded; (2) a decrease in the discharge; (3) a cleaning of the tuberculous ulcer. As early as eight days after the commencement of a spleen diet the base of the ulcer, which had hitherto been covered with a whitish-gray surface, began to show everywhere fresh, healthy, red granulations. This sinus which before had the appearance of having been stamped out with a stamping iron, and had an undermined margin, lost its malignant appearance, filled up, and became 'full' and decreased visibly in size; (4) the swelling around the sinus decreased; (5) the pain and sensitiveness in the joint were relieved; (6) the general condition showed a remarkable improvement. The gray pallor of the face had yielded to a healthier tone. There was an increase of appetite, and the patients, especially in the case of children, became more active and lively, and quickly put on weight. Of the fifteen cases under observation, only two failed to respond to treatment. Five are completely cured."

F. Mattausch, of Vienna (*Beitr. z. Klin. d. Tuberk.,* Oct. 23, 1930, lxxv, p.597), claims to have used spleen extract with success during a year and a half in the treatment of 140 persons with pulmonary tuberculosis. Roentgenograms of several patients taken before and after the treatment show definite indurative changes. Following spleen therapy there occurs what

Mattausch calls "the stabilization of the defense powers of the patients," as shown by the disappearance of the deviation to the left and the appearance of lymphocytes and eosinophiles in the leukocyte picture.

These reports of good results with spleen diet in severe, febrile tuberculosis prompted J. Leitner, of the Sanatorium in Reiboldsgrün, Germany (*Deutsch. med. Wchnschr.*, Dec. 5, 1930, lvi, p. 2082), to employ spleen extract in the treatment of forty-one tuberculous patients. Thirty-five of these patients were in the third stage of the disease, and six were in the second stage. Bacilli could be detected in all cases, and thirty-six had cavities of varying extent. In fifteen of the patients the larynx was involved—truly a hard series.

Each day these patients were given an amount of spleen extract equivalent to 120 Gm. of fresh spleen, and the treatment was continued for from six weeks to five months. Twenty-four of the forty-one patients were not benefited. Of the other seventeen, one with exudative tuberculosis showed a marked improvement: weight increased, temperature decreased, and the pulmonary process became latent. Sixteen showed improvement, particularly in the general condition, such as increase in weight and decrease in temperature. In some cases, there was also a decrease in the coughing and in the quantity of sputum. The pulmonary process became only temporarily stationary, showing no improvement, and the laryngeal processes were not influenced. The results obtained by Leitner with spleen therapy were not so satisfactory as those reported by other investigators; but, because the treatment is never harmful and in some instances gives beneficial results, he says that a trial is justified, especially in those cases in which other therapeutic methods cannot be used.

Any remedy that is suggested for the treatment of tuberculosis is bound to be misunderstood, because the tendency of the profession is to depend on one given measure rather than to consider it as only a part of a method. Of course, spleen therapy does not cure tuberculosis, but I firmly believe that it produces some subtle improvement in the resistance which apparently accentuates the utility of the associated measures.

THE REGULATION OF LIME IN THE TISSUES—In 1923 I became interested in the possibilities of modifying the blood calcium by parathyroid therapy as then outlined in several articles in the medical literature. I referred to the work on the spleen that had been done years before, and tried to find some connecting link between the parathyroids and the spleen (effectively demonstrated later by John C. Brougher, of Vancouver, Washington—see p. 182), especially since several physicians were developing parathyroid therapy as an adjunct in the treatment of tuberculosis, with encouraging results.

In the meantime, a good deal of study had been given to the blood calcium in tuberculosis and also to the influence that various organotherapeutic products have on blood calcium in experimental laboratory work and in the clinic. It is evident that some cooperative factor associates the functions of these organs and that each has a part in the fighting powers of the organism.

Since the perfection of the parathyroid hormone, attempts have been made to demonstrate its influence in the tuberculous. At the Jefferson Hospital, in Philadelphia, Burgess Gordon and A. Cantarow (*Am. Rev. Tuberc.*, Dec., 1929, xx, p. 901) observed a series of cases from the standpoint of the effect of parathyroid extract and lime on calcification and healing in tuberculosis. The results were not decisive, as will be seen below:

"1. A Roentgenographic study of sixty tuberculosis patients to whom parathyroid extract was administered (10 units twice daily), from one to four months, showed no specific change in the course of the disease except as obtained through the relief of signs and symptoms, notably hemoptysis, pleurisy, cough, and expectoration. There was no evidence of decalcification or increased calcium deposition in the lungs.

"2. Parathyroid extract (20 units every 48 hours) and calcium lactate (30 gr. three times daily) were administered to fourteen patients with pulmonary tuberculosis for a period of from one to six months. The results were similar to those noted in the first group. Roentgenographic studies failed to reveal any change in calcification of the lung-fields or bones of the hands, and there was no visualization of the blood-vessels.

"3. It appears that diseased or potentially diseased tuberculous tissue is not influenced directly by hypercalcemia and that parathyroid hormone and calcium should not be administered with the expectation of inducing calcification. The influence of these agents on certain phenomena arising during the course of the disease may be considered of value in treatment."

LIME STARVATION AND COLLOIDOGENESIS—Attention has been called to the frequency with which calcium is lost in the tuberculous patient, and the phrase "lime starvation" is now often used. This condition is the rule, even in early cases. In fact, some years ago a French clinician actually suggested a urinary test for tuberculosis—a quantitative measure of the excessive loss of calcium so usual in these cases. As we have seen, there are two endocrine aspects of this involving (1) the spleen and (2) the parathyroids. Within the last few years these supposedly unrelated services have been found to be closely related, as already outlined.

For a moment let us recapitulate Charles Bayle's philosophy of colloidogenesis. This persistent clinician through the years—I have followed his work personally for twenty years—has believed and demonstrated that there is a difference between the minerals that we ingest and those *in* the tissues.

There is, of course, the well-known physical difference between crystalloid and colloid. Bayle has shown that there is a subtle factor that assists in the colloidogenesis of minerals, as well as another detrimental factor, equally subtle, that interferes with the maintenance of the body's minerals in a colloidal or humanized state.

As soon as this malign factor overbalances the beneficent one, the needed minerals begin to be lost, for they give up their colloidal status, become crystalloid, and the body eliminates them as foreign material. The colloidogenic factor is believed by Bayle to be in the spleen, and the Chaix spleen product, *Colloidogénine,* has been used successfully in France for many years.

Having seen some of Bayle's countless protocols (of his work with rabbits and guinea-pigs), when the reports of Vines came out in 1923 (*New York Med. Jour.,* April 4, 1923, cxvii, p. 412), I was curious about the prospect of parathyroid therapy in tuberculosis. My experiments were sufficiently conclusive to warrant the addition of a spleen concentrate to a parathyroid formula that I had been using for years. The outcome was Para-Spleen Co.,* which has given me excellent service in chronic ulceration of every description (95). Then came F. S. Hammett, of Philadelphia (*Am. Jour. Anat.,* May, 1927, xxxix, p. 239), who, in studying the relation between the parathyroids and the spleen, stated that the latter is specifically affected by parathyroid deficiency with a tendency toward hypertrophy. His studies were followed by those of J. C. Brougher (*Am. Jour. Physiol.,* April, 1930, xcii, p. 648), on recovered thyro-parathyroidectomized animals following splenectomy. Of these he says:

"From the preceding results it would appear that some dependent relation exists between the serum calcium and the parathyroids and spleen.

"The fact that serum calcium dropped following splenectomy and showed no change in other laparotomies points to a specific action of the spleen on calcium metabolism.

"The occurrence of tetany in recovered thyro-parathyroidectomized animals following splenectomy might be interpreted to mean that the spleen had, to some extent, taken over the function of the parathyroids. Whether the removal of some other organ such as the liver would also produce tetany cannot be stated."

To say that parathyroid and spleen constitute a remedy for tuberculosis would be unfair; to suggest that it has any effect on tuberculosis per se would be stretching the truth; but to add that colloidogenesis and calcium fixation are worth considering in tuberculosis is straightforward and true. With the experimental evidence and clinical confirmation that are abundantly available, I believe that we are justified in telling these facts.

THE ADRENALS AS FATIGUE FACTORS—There is another important endocrine aspect of tuberculosis. The "tired, tired, tired" plea of the tuberculous naturally draws attention to the adrenal glands. As hypoadrenia is born of toxemia, how can a patient with tuberculosis avoid it?

If the reader will study three or four chapters in this section—on Hypoadrenia (35), Malnutrition (43), Convalescence (48), and Neurasthenia (77), he will find many points in common with the clinical picture found in patients with chronic pulmonary tuberculosis. These similarities direct our attention to the same fundamental trio of troubles: chronic toxemia, endocrine depletion, and malnutrition.

The consideration of the endocrine aspects of the tuberculous patient was first given aggressive emphasis in France, nearly thirty years ago, when Emile Sergent, of Paris, began to connect the asthenic picture of tuberculosis with *l'insuffisance surrénale* (hypoadrenia). As the years went by, this relationship grew on him until in 1920 he published a 700-page book on the subject entitled "Etude clinique sur la tuberculose" (Paris, A. Maloine et Fils).

A lucid explanation of the relation between the adrenals and tuberculosis was given recently in an editorial in the *Medical Herald* (May, 1931, l, p. 193), from which the following is taken:

"For some years, careful blood-pressure studies have been done routinely in tuberculous patients, and it has been found that low blood-pressure serves as a guide to the amount of toxic absorption. Discussing a paper on the endocrinology of tuberculosis before the Royal Society of Medicine, Halls Dally said that, as toxemia increased, the arterial pressure was lowered, but, when toxemia diminished or ceased, then both systolic and diastolic pressures rose. When toxemia increases, the pressures will coincidentally fall, and if they continue steadily to fall the prognosis becomes very grave. However, with improvement, or if the tuberculous condition becomes stationary, the pressures gradually rise and the pulse pressure increases, indicating a heightened defensive reaction on the part of the patient.

"Some time ago, the late Charles E. de M. Sajous explained a good many phases of the tuberculosis problem by their association with the adrenal system. A predisposition to tuberculous disease is, in his opinion, always associated with adrenal deficiency, which increases with the progress of the disease until, finally, an actual failure of the adrenal apparatus may result, which is, of course, fatal. The asthenia and excessive fatigue characteristic of patients with well-established pulmonary tuberculosis are evidences of adrenal inadequacy, and therefore quite rationally point the way to treatment that should be successful. While Sajous himself did not suggest deliberate adrenal therapy, it may properly be deduced from his remarks, and other physicians have definitely advocated this therapy. Emile Sergent, who has written voluminously on adrenal insufficiency, asserts that adrenal therapy is always useful in the treatment of tuberculosis. It counteracts the fatigue,

the anemia, the muscular atrophy, the arterial hypotension, and the tendency to vomiting, which are frequently observed in these patients. In Sergent's opinion, adrenal therapy should be administered to all tuberculous patients whose digestive organs will accept it. Separately from total adrenal therapy, he employs epinephrine as a cardiac tonic and also as an adjuvant in the treatment that is administered for the purpose of bringing about remineralization, especially an improvement in the calcium metabolism.

"In the opinion of T. Silvestri, an Italian physician, adrenal therapy counteracts the loss of calcium that is suffered by tuberculous patients and is superior to the administration of calcium preparations alone. In fact, he says that if calcium therapy is good, then adrenal therapy is better, and the combination of the two is excellent. One of the important effects of adrenal therapy is the neutralization of toxins, which it brings about with resulting clinical improvement. Silvestri's opinion is supported by Pierre Lereboullet, who found that the tuberculous process was surprisingly benign in several patients who had been given several courses of adrenal therapy over a period of years. There is no contraindication to the administration of adrenal substance in pulmonary tuberculosis, but it is well to be cautious in patients who are subject to hemoptysis."

The writings of Sergent teem with references to the adrenals and tuberculosis. He is convinced of the uniform frequency of this clinical relationship, and his convictions are confirmed by many therapeutic experiences. The following paragraphs translated from one of Sergent's other books, "Etudes cliniques sur l'insuffisance surrénale" (Paris, 1920, A. Maloine et Fils, p. 417), are of interest:

"You will find also a large diagnostic element in the results of organotherapy. I have observed a certain number of persons in whom I have, in this fashion, proved absolutely the adrenal origin of these findings. These facts are of great practical importance because you can, if you wish, institute a useful therapeusis. You will not use adrenalin, but the total extract of the adrenal gland. I have been in the habit of using ordinary, relatively small doses representing perhaps 30 cg. of the desiccated powder. If this produces neither vertigo nor headache, I rapidly increase the dose to 60 or even 90 cg. a day. This intensive medication ought not to be continued for a long time. It is preferable to push the dose for eight or ten days, separated by intervals of equal length.

"Of course, our investigations should not be limited to these matters. You should always study the arterial tension so as to know when to stop if there is a relatively too rapid increase in the tension. On the contrary, if the tension falls, the treatment should be pushed. You will often be pleased to find that a low tension has been increased decidedly, and to see a progressive attenuation of the usual symptomatology of general adrenal insufficiency, particularly the asthenia and malnutrition.

"Do I believe that this has a direct action on the tuberculosis itself? Evidently it does not; at least, not directly. In raising the general response

of the individual and in putting him into a better general state, you are helping the fight and raising the efficacy of the body's powers to control the actual tuberculous infection. The good effects of this practical method have been confirmed by Renon, Gouraud and Paillard, and Lereboullet. It goes without saying that the usual routine treatment of tuberculosis ought to be instituted at the same time as the adrenal support."

The discovery of the adrenal cortex hormone has renewed the interest in the possibilities of adrenal therapy as an adjunct in the treatment of the hypoadrenia of tuberculosis. For further information see Hypoadrenia (35).

THE DEFENSES AGAINST TUBERCULOSIS—In a consideration of latent tuberculosis and its relation to the endocrine glands, H. Sewall, of Denver, Colorado (*Am. Rev. Tuberc.*, Jan., 1920, iii, p. 665), said:

"The intoxication is manifested not by pulmonary signs and symptoms but by insufficiency of one or more of the other vital organs, especially those of the internal secretions. I have under observation persons of this class in whom deficiency in the secretions of the pituitary, adrenal, and thyroid glands, respectively, is strongly evidenced by their pronounced clinical improvement under the administration of the appropriate gland products."

In the consideration of malnutrition (43), special attention has been called to the facility with which nutritional defects pave the way for tuberculous infection. That these defects are essentially endocrine in character will be evident to all, for, as E. M. Ellison has well said (see page 310), "Children surely need the proper stimuli from their endocrine glands to develop their vital activities."

THE IMPORTANCE OF DYSOVARISM—Ovarian dysfunction puts a stress on the body as a whole, including the endocrines. Every woman who has difficulty with her menstruation suffers from malaise, asthenia, and a period of depletion of greater or less length and degree, depending upon the extent of the involvement. Many women are seriously ill for a few days each month, during which time the defenses of the body are obviously lowered. They are subject to colds or other infections; they develop skin irritations or boils, and in many ways emphasize the conclusions already outlined (68) connecting the endocrine glands with the immunizing response.

It is impossible to consider a series of tuberculous women without being made decidedly aware that ovarian dysfunction causes a monthly setback in the recovery from the tuberculosis. Obviously it is as rational to attempt to regulate menstrual irregularities in tuberculous patients as in those not suffering from tuberculosis. An extended clinical experience confirms the advantage of attending to the endocrine upsets associated with dysovarism as a part of the treatment of all these cases.

Some years ago, E. Coulaud, of Paris, carried out a series of studies with the tuberculin skin test in a number of patients. He concluded that there is a diminution of sensitivity to tuberculin, which apparently is coterminous with a lessening of immunity during several days each month.

In a certain California tuberculosis sanatorium eight nurses, all of them with arrested tuberculosis of varying extent, were studied from the standpoint of menstruation. In seven, the regulation of the customary thyro-ovarian-pituitary dysfunction (with Thyro-Ovarian Co.*) caused symptomatic improvement extending far beyond the actual menstruation itself. The average gain in weight was 11 pounds, and the improvement in strength and resistance was particularly noticeable during the period of greatest stress, that is, prior to and during menstruation.

At the Olive View Sanatorium (Los Angeles County Tuberculosis Sanatorium), Emil Bogen carried out a careful investigation of the exciting factors in tuberculous hemoptysis, which indicated, among other things, a close relation between the incidence of pulmonary hemorrhage and menstruation.

The following table giving data from thirty-six patients is peculiarly suggestive (*California and West. Med.*, July, 1930, xxxiii, p. 473):

Table 20. — *Menstruation and Hemorrhages*

Before menses	11
During flow	13
Following week	1
Intervening two weeks	4
Menses absent	7

From this, it will be noticed that in only five, or 14 per cent., of these thirty-six patients, the hemorrhage is in no way connected with the menstruation or amenorrhea. Bogen's comments on these statistics are of interest:

"Examination of these reports showed a very definite relationship. In only one case did hemorrhage follow the menstrual flow, and in only four did it occur during the intervening fortnight. More than 85 per cent. of the women reported that hemorrhage came either during a period of amenorrhea, or preceding or accompanying the first few days of menstruation. In several instances the observation was made that hemorrhage was apt to come at the time of suppression of menses, the so-called vicarious menstruation. Whether the hemorrhages so occurring depend on changes in the coagulability of the blood, on the engorgement of the mucous membranes of the lungs similar to the observed engorgement of the nasal mucosa, or on some specific expression of the female sex hormone, is not known."

Elsewhere attention has been called to the comparative frequency with which amenorrhea occurs in tuberculous girls and women (80). This incident may be judged in two ways: (1) The amenorrhea is a protective measure

to spare the organism from depleting losses of much-needed blood, and (2) it is directly due to defects in the mechanism responsible for initiating and maintaining the menses and, therefore, a sign of a disorder that should be regulated. I believe that the second of these opinions is the more important, and I am opposed to the suggestion to let well enough alone in these cases. It should be remembered that the endocrines responsible for regulating the menses have other important duties which it is legitimate to presume are as poorly done as the one under discussion. Hence, functional amenorrhea in the tuberculous is an indication for aggressive organotherapeutic interference, as mentioned above and discussed more fully in my consideration of Dysovarism (80).

TUBERCULOSIS AND THE PANCREAS—A fact that has impressed many clinicians is that tuberculosis frequently complicates diabetes, especially diabetes of pancreatic origin. For example, C. M. Montgomery, of the University of Pennsylvania (*Am. Jour. Med. Sc.,* 1912, cxliv, p. 543), gave the results of his study of 117 cases of diabetes, from which he concludes that resistance to the tubercle bacillus is lowered in diabetes, and that a large number of diabetics eventually develop a very acute, extensive, and rapidly fatal form of pulmonary tuberculosis. This investigator notes that when diabetes and tuberculosis appear together, it is the diabetes that is usually primary.

Many facts seem to establish conclusively that, when the internal secretion of the pancreas has been lost or diminished either experimentally or from pancreatic disease, there is always a noticeable reduction in the power of the organism to destroy bacteria. Quoting further from the editorial in the *Medical Herald,* already referred to:

"Pancreas therapy is advocated by Scheffler for the special purpose of encouraging a gain in weight in the patients. Some tuberculous subjects are always emaciated, even though their pulmonary condition is improved. In these patients, results of pancreas therapy are said to be often very remarkable. Pancreas therapy thus is an adjuvant treatment that does not influence the tuberculous process itself or the systemic reaction to the tuberculosis, but merely improves the patient's nutrition and encourages his gain in weight."

Hence, the treatment of pancreatic insufficiency is worth considering as a nutritional measure in tuberculosis; and, whether the benefit is direct, *i.e.,* upon the immunizing response (68), or indirect, *i.e.,* upon nutrition itself (43), this offers us one more point from which to attack the problem. A pancreatin product known as Panteric Tablets (Sansum) is of service in this respect. Generous doses of pancreatin facilitate the pancreatic digestion and correspondingly increase the nutrition and bodily defenses.

95. ULCERATION

The Calcium Balance and Healing—Parathyroid Therapy in Leg Ulcers —Extending the Method to Other Ulcers—The Cause of Hypocalcemia— Early Trials in America—The Control of Sprue—The Routine Procedure.

SINCE 1926, the growing appreciation of the relation between chronic ulceration, lime fixation, and parathyroid therapy has put a completely new aspect upon the prognosis of old chronic leg ulcers, and, indeed, almost any ulceration.

THE CALCIUM BALANCE AND HEALING—Like the coagulation of the blood, the healing of wounds depends upon the presence of a suitable amount of lime in the blood. Defects in this vital factor handicap the body in its healing capacity, and ulceration results. This fact is not scientifically demonstrable, and it has not been proved experimentally. The subject has been developed in the clinic, although, of course, it has been known for the last fifteen years that the parathyroid glands regulate the body calcium, and laboratory and clinical experiences alike have confirmed the relation that deranged calcium metabolism bears to chronic septic or ulcerative conditions and the potency of parathyroid therapy in modifying both the calcium imbalance and the associated ulcerous manifestations.

PARATHYROID THERAPY IN LEG ULCERS—Here is one of the most startling and at the same time most casual of the advances in endocrine therapy: As H. W. C. Vines and his associates, at Cambridge University (*Brit. Med. Jour.*, May 20, 1922, i, p. 791), were studying the calcium metabolism, they happened to note that the calcium index of the blood was uniformly low in a series of patients who had ulcers of the leg—chronic, intractable areas of necrosis, which for years had been resistant to all sorts of local and general treatment. The condition, known as *status calciprivicus* or hypocalcemia, was found to be much more common than had been supposed, and they sought a means whereby they could build up this abnormally low blood-calcium index.

The work of a number of earlier investigators, notably W. G. MacCallum, now of Johns Hopkins University (16), having demonstrated that the parathyroid glands have a remarkable control of calcium metabolism, it was logical to try to influence this factor by homostimulative organotherapy. It was hoped, by the oral administration of parathyroid, to encourage the function of these glands and thereby modify the chemistry of the body that is under their control.

Vines' clinical studies outlined in his book ("The Parathyroid Glands in Relation to Disease," London, Edward Arnold & Co., 1924, p. 31) brought to light the fact that there are two types of calcium deficiency: one in which the active or *ionized* calcium is lessened without any marked alteration of the total amount, and another in which the *total* calcium is diminished. In the acute and chronic septic states, the element is usually within normal amounts but in a form that cannot be utilized by the tissues. In the relatively uncommon cases of spasmophilia and tetany, there seems to be an excessive excretion of calcium, resulting in calcium starvation of the tissues.

When the calcium balance was reestablished in these patients with chronic leg ulcers, the sores began to heal. Scores of cases were treated with really remarkable results, and thus an entirely new field for organotherapy was opened.

EXTENDING THE METHOD TO OTHER ULCERS—As a result of these experiences, the study of the calcium balance has been given still greater prominence, and the laboratory investigations have been extended to other disorders in which the same underlying chemical pathology was expected.

It was only natural for those who had used this new treatment of leg ulcers to presume that, since these ulcers were associated with low blood calcium, other ulcerous conditions should be studied from this standpoint with a view to submitting them to experimental parathyroid treatment. Consequently, later experiences included every variety of ulceration—chronic otitis media, ozena, sinusitis and catarrh, gastric and duodenal ulcers, intestinal ulceration such as sprue and mucous colitis, severe burns and bedsores, corneal ulcers, and tuberculosis. This is truly a remarkably varied list of troubles to be treated with any one remedy. Nevertheless, our present opinions are not based on speculation but on an extended clinical experience to which attention already has been called in several earlier chapters.

Practically every case in which the blood calcium was studied presented the typical calciprivic picture. In many instances, trials with parathyroid therapy brought about a more normal calcium picture with coincidental benefit to the ulceration, just as it did in the original experience with leg ulcers.

THE CAUSE OF HYPOCALCEMIA—Vines and Grove have shown that the principal cause of the picture that they have been studying, which undoubtedly must include hypoparathyroidism, is chronic sepsis. Whether the parathyroids permit the sepsis, or whether their dysfunction results from it, is quite immaterial. The important point is that we have learned that

parathyroid homostimulation produced by oral administration of active parathyroid preparations will, in suitable cases, change the blood-calcium index and hasten healing in old ulcers.

We all realize, of course, that an ulcer is more than a local, lowered resistance complicated by the bacteria that may be present. It is apparent also that an ulcer of the leg is somewhat different from an ulcer of the stomach or duodenum, for conditions in the actual ulcer can be controlled more easily on the leg than in the stomach. But, despite the interference of the alimentary contents, these and other ulcers have been cured by parathyroid organotherapy, which constitutes a most remarkable advance in the therapy of a discouraging medical problem.

EARLY TRIALS IN AMERICA—When I returned from England (in 1926) I was most anxious to test Vines' new ideas. Already an unusually potent parathyroid product had been in use in Parkinson's disease (81), and I was in a position to arrange for a prompt trial of the method. The reports that came in sounded like some of the experiences of "Alice in Wonderland." One of the first ones was from Fresno, telling of a man, aged sixty-eight, with an extensive leg ulcer that had defied treatment for twenty years. In fact, this man had decided to part with his leg, and his physician had agreed to operate when his attention was directed to the Vines method. In two and a half weeks healing was so advanced that the patient left the hospital, and his improvement continued until healing was complete.

Another remarkable report from the same city is typical of many that have accumulated through the years:

"A. M. K., age fifty, a night clerk in a hotel, had a deep ulcer completely covering the left leg from about four inches below the knee to the ankle. This large area was covered with a thick, foul-smelling exudate. The foot was very edematous and the whole leg seemed swollen. There was much pain. Various local and internal measures had been tried for three years with only occasional, slight improvement that never lasted. Local treatment was continued (chlorazene followed by a parresine dressing) plus the suggested formula, 1, q.i.d. In seven weeks the leg was completely healed, the edema had disappeared, and the man had gained fifteen pounds during the treatment. The progress has been remarkable considering the large area involved and the long duration of the illness. Incidentally, the patient did not lose a single night's work during the treatment."

As with other forms of treatment, workers with parathyroid have been led, first by one interesting experience and then another, into new fields in this almost virgin territory. Many seemingly dissimilar conditions were treated—conjunctivitis at first thought does not seem to have much in com-

mon with sprue, nor bed-sores with consumption, but on second thought one can discern an underlying relationship.

THE CONTROL OF SPRUE—One of the conquests of parathyroid therapy is the oriental alimentary disease, sprue. First used in Hongkong by H. H. Scott (*China Med. Jour.*, July, 1923, xxxvii, p. 581), the therapy has been employed extensively in the Far East, Great Britain, and the United States. I have personally treated two cases with decisive success. Several excerpts from the literature and other pertinent information will be found elsewhere (53). Suffice it to say that the oral administration of Para-Spleen Co.*—1, q.i.d. or 2, t.i.d. for sixty days—has cured extensive alimentary ulceration of maximum degree, visible in the mouth and sigmoid, and apparently involving the entire tract. Incidentally, in the more severe of my two cases, a frontal sinusitis of years' standing was cleared up simultaneously.

THE ROUTINE PROCEDURE—At first, the treatment of ulceration was the same as that of Parkinson's disease. As the spleen was found to influence the blood calcium (21), however, spleen substance was added to the parathyroid. The resulting formula, Para-Spleen Co. (1927), has been used successfully in many thousands of cases of ulceration of almost every description. It has been of service in a great many cases of paralysis agitans, tetany, and leg ulcer. It has been beneficial in cases of gastric ulcer and chronic running ear. It has cured sprue as if by magic.

The usual dose is 1 sanitablet at meals and at bedtime, representing a daily dose of 1/5 gr. of the true parathyroid desiccation. Treatment should be continued for three months, for it is not good policy to give this product for only a few weeks although it may be helpful within such a short time.

To recapitulate: There has been outlined here a method of curing ulcers of the leg, chronic otitis media, and several fundamentally similar conditions, including ulcers of the sinuses and the alimentary tract. This method has been found of considerable prospective adjuvant service also in the treatment of tuberculosis, since it appears to be based on sound physiological and chemical foundations (94).

96. UTERINE DISEASE

Utero-Ovarian Hypoplasia—Sterility—Infertility or Spontaneous Abortion—Uterine Fibroids—Uterine Malignancy—Metrorrhagia—Erosion of the Cervix—Leukorrhea—Uterine Subinvolution.

THE FUNCTION and service of the uterus are so intimately involved with the endocrine activities that for all our purposes the uterus might be included in the endocrine system. In fact, some writers are now doing this, and are combining the utero-ovarian and placenta-luteal mechanisms into two organizations—the one serving a certain broad purpose in ordinary circumstances, and the other in the extraordinary condition of pregnancy. Some suggestions have been made that the uterus itself is an actual organ of internal secretion with one or more hormones that contribute to the balance that the utero-ovarian system maintains with the other endocrine glands.

Since the circulation and nutrition of the uterus are under the same hormone control as the ovaries, one cannot have uterine hypoplasia with normal ovaries, or vice versa. Further, the known effects of the thyroid and pituitary on the ovarian function involve the uterus also. So uterine dysfunction really should not be considered apart from dysovarism, for the two are inextricably related. However, there are some features of uterine disease to which separate attention will be given here.

UTERO-OVARIAN HYPOPLASIA—The utero-ovarian hypoplasia found in infantilism, like the same picture without other marked evidences of infantilism, is now looked at as a very different problem from what it was only a few years ago.

There are two types of infantile uteri that are of interest for the moment: (1) the utero-ovarian or pelvic type, in which the hypoplasia seems to involve the uterus and adnexa without the expected changes in the secondary sex characteristics (see Infantilism as a pituitary feature—83), and (2) the general type in which the pelvic changes are a part of a much more obvious picture that is the result of extrapelvic dyscrinism.

The former is treated as a uterotrophic matter with Plestrin* (11), the female sex hormone, while the latter is chiefly a pituitary or thyro-pituitary problem which also requires treatment from the standpoint of the associated glands.

The discovery of the remarkable trophic effects of the estrins from the ovaries (graafian follicles), the placenta, and the anterior pituitary has revolutionized the treatment of utero-ovarian hypoplasia and sterility in particular.

STERILITY—Functional sterility in the female may be due to a number of causes that have nothing to do with the glands of internal secretion. We cannot concern ourselves with these save only to mention several of them: (1) occlusion of the fallopian tubes; (2) uterine malpositions; (3) cervical stenosis; and (4) chemical abnormality of the vaginal fluid.

Infantilism of the ultimate pituitary or thyroid type, with hypogenitalism, total amenorrhea, and the female analogue of eunuchoidism, is properly associated with sterility; and the incapacity to reproduce is a protective measure on the part of Nature which should not be interfered with.

There is another form of sterility that is quite commonly associated with ovarian insufficiency, amenorrhea, and the endocrine imbalance that brings about utero-ovarian hypoplasia. These conditions frequently respond to endocrine intervention, which assists in the reestablishment of the endocrine regulation of the functions involved. This subject is more fully considered as a form of ovarian dysfunction (80).

One of the principal exhibits in the pageant of endocrine accomplishments is the female sex hormone. Its spectacular influence in the laboratory has directed attention to a method of treating sterility that is apparently more nearly specific than anything previously available. This statement is made even in view of the fact that, before its perfection, numerous cases of dysovarism associated with amenorrhea, menstrual irregularity, and sterility had responded in all three of these aspects to the indicated organotherapy.

As has been seen (11), the trophic influences of this female sex hormone are peculiarly marked. For example, a series of injections over a period of four weeks causes an increase of from 1000 to 1500 per cent. in the size of the entire sex mechanism of immature rabbits, and the animals have been brought into heat well in advance of the usual time of maturity.

Senile animals also, whose reproductive capacity evidently was over, have been made fecund again; and, following a similar course of treatment have borne one and sometimes two "postclimacteric" litters.

In view of the decisive trophic influence of Plestrin, its chief therapeutic indications are infantilism and conditions of a hypotrophic nature in which there are defective nutrition and growth of the ovaries and adnexa. With the trophic changes brought about in the actual pelvic structures there comes a change in fecundity, and this has been demonstrated in several clinics. In fact, some physicians consider Plestrin to be the most satisfactory remedy for sterility associated with utero-ovarian hypoplasia. For example, in a series of more than three hundred cases in one California clinic, the successes have reached beyond 60 per cent.

For reasons that will be clear, the female sex hormone is of no value in the control of thyroid, pituitary, or other endocrine difficulties that may be associated with dysovarism and sterility. On the other hand, its effect upon trophic ovarian insufficiency, primary amenorrhea, and sterility, is often remarkable. Treatment of conditions of this nature must be carried out for several months, the average course consisting of from forty to sixty 1-cc. doses (each containing 25 Doisy rat units) which are given intramuscularly every other day.

It has been suggested that these injections might be given in an irregular fashion, pushing the dosage (25 to 50 units daily) for several days prior to the expected menstruation or molimen, and discontinuing it for a brief pause after this has passed. It is not yet established that this cyclic variation of the dosage is an advantage, as it undoubtedly is in the routine treatment of dysovarism.

Stimulating doses of X-ray are sometimes used to arouse ovarian activity in amenorrhea and sterility, and there can be no discounting the reports. However, due either to a special sensitivity to the rays or to overdosage, several unexpectedly bad results with the loss of what little menstrual ability the patient previously had, have convinced me that this procedure is one of the very last to be attempted.

INFERTILITY OR SPONTANEOUS ABORTION—German students of the subject differentiate a form of sterility to which they give the name "infertility." The condition is really a form of spontaneous abortion in which the fertilized ova are habitually lost. It is suggested that the bedding of the ovum is unsuitable and that the nutritional, and presumably endocrine, factors necessary to nidation are faulty.

Habitual abortion has been brought about mechanically by complete laceration of the cervix. Then there are some infectious diseases and intoxications, especially syphilis and tuberculosis, that frequently are responsible for habitual abortion, as are also constitutional affections such as diabetes and deficiency diseases, because of the absence of certain vitamins in the diet.

From the standpoint of functional endocrine imbalance, a number of conditions may bring about spontaneous expulsion of the fetus. Thus menorrhagia may cause early loss of the ovum, owing to an insufficient restraining effect of the corpus luteum upon ovarian activity. Habitual abortion has been said to be the result of deficient development of the corpus luteum during early pregnancy. There will be found in the literature several reports indicating that corpus luteum therapy has been used with advantage in the control of habitual abortion. In cases of ovarian and uterine hypoplasia,

nidation of the fecundated ovum is usually unsuccessful. Undoubtedly the factors regulating the growth of the uterus influence nidation also.

There are a number of reports showing that miscarriage frequently is due to the subthyroid state. A deficiency of calcium may be a cause of sterility and habitual abortion in the mother and of tetany in the new-born. These conditions are properly treated with thyroid and parathyroid medication, respectively. It has been suggested that sensitiveness to placental products that have entered the circulation may be responsible for abortion. This seems logical when it is remembered how seriously the mother's strength may be impaired by vomiting of pregnancy of placental origin. This explains why the administration of placental substance has been employed successfully in threatened abortion as well as in extreme hyperemesis (84). These two conditions have been attributed to an upset in the carbohydrate metabolism, which, to some writers, indicates a pituitary insufficiency.

Further, it may be that an allergy on the part of the wife's organism to, or an intolerance of, the husband's sperma will result in either complete sterility or an early abortion. Defective spermatozoa may retain sufficient vitality to cause conception but not enough to allow it to proceed beyond a certain point of development. Finally, abnormalities in the ovum itself may be the cause of abortion.

The treatment of hyperemesis with Placenta Co.* (84) or with injections of corpus luteum or of the compound solution known as Placento-Luteum,* or both, has been so effective in controlling many problems of early pregnancy that a number of physicians have been led to use it in women who previously had failed to carry a fetus for more than from six to twelve weeks. Several of the reports are enthusiastic. It must be remembered, however, that other factors might have been responsible, for there is no way of knowing that the etiological interference originally responsible for the difficulty has not been controlled since the last unpleasant experience.

UTERINE FIBROIDS—Fibromyoma uteri is a disease in which there is a hypertrophic change in the musculature of the uterine walls with the development of true new growths or myomata. These tumors may surround a nerve, causing much pain; they may degenerate and thus be a source of chronic toxemia; or they may become malignant. In my estimation, eradication is the best treatment, for it avoids all these sequelæ.

Since in most cases surgery of a fibroid should include the whole uterus, the magnitude of the operation often militates against the decision. Then, too, the symptomatology often is not serious enough to warrant extreme measures; and there are several ways to temporize, especially when one is

encouraged by the fact that the normal uterine involution expected at the menopause has been known to influence the fibroids as well. None the less, surgery is the best therapy—better considerably than radium or X-ray.

But this is supposed to be a consideration of the endocrine aspects of fibroids, which in this instance have to do with the clinical possibilities of organotherapy; and these, it safely may be asserted, are real enough.

Since the principal symptom of fibroids is menorrhagia, the treatment usually recommended for that menstrual disorder has been used in fibroids also. In fact, there is quite an extensive literature on the subject going back as far as thirty years. Quoting from my earlier book, "Practical Organotherapy" (1922, page 216):

"More than twenty years ago, Robert Bell discovered that mammary extract exerted an influence on uterine fibromata which caused a recession in their size and a reduction or cure of the menorrhagia. Feodoroff, of Petrograd, has written many reports on the subject and enthusiastically advocates this treatment. As a matter of fact, reports enumerating more than a hundred cases in all might be collected from the literature extolling mammary extract as a curative remedy for this condition. . . . I prefer not to urge mammary preparations as a means of remedying fibroids, but rather to recommend their use in the functional conditions such as show themselves in menorrhagia, etc., but I will not deny that there is a possibility that if this treatment, preferably perhaps Mamma-Pituitary Co.,* is used to control the hemorrhagic feature of the fibroid syndrome, there may be a very pleasing reduction in the size of the uterine tumor, besides the expected benefit to the menorrhagia.

"W. A. Briggs, of Sacramento (*Calif. State Jour. Med.,* Sept., 1917, xv, p. 354), reports his experiences which were quite encouraging. He believes that the mammary hormone probably antagonizes the uterine stromal hormone, thereby modifying or preventing an excessive hyperemia and thus controlling menorrhagia and the local nutrition of the uterine tissue (fibroid). The effective dosage depends on the degree of hyperovarism. I learn from a physician in Mexico that the Mamma-Pituitary Co. has been used by him for six months in a woman with 'inoperable fibroid,' with hemorrhages, malnutrition, and a heart which precluded surgery. He writes: 'The excessive flow has been entirely controlled, the patient is better in every way, and the fibroid is reduced fully one-half.'"

A physician writes from Brooklyn, New York:

"I am submitting clinical reports of two cases of uterine fibroids in which I have used successfully the pluriglandular formula, Mamma-Pituitary Co.:

"Mrs. M., age fifty-two, widow six years, the mother of three healthy grown children, consulted me during April, 1921, for profuse metrorrhagia and menorrhagia. She said that she always flowed excessively during her periods, which were always regular, but that for the preceding six months

the flow had become alarmingly worse. Pelvic examination revealed a hard, fibrous mass the size of a large orange in the region of the left broad ligament. I advised that she have a hysterectomy done promptly. She said that this advice was not new to her, as several other physicians had advised her likewise; but, as she would not consent to the surgery, I put her on Mamma-Pituitary Co., 1 or 2 tablets every four hours as needed. When she consulted me two weeks later, she informed me that the remedy worked like magic and that her flow had almost stopped. This patient was under observation for several months, and the last pelvic examination revealed a very much shrunken mass in her left broad ligament. Neither metrorrhagia nor menorrhagia was present, but a normal menstruation that lasted for five days. The general health was excellent.

"Mrs. S., to whom I was called during January, 1921, had been flowing for three weeks. Ordinary hemostats seemed to increase the flow. She was given Mamma-Pituitary Co., 2, every three hours, and was put to bed. After the second day the flow became less, and continued to diminish until, after she had been in bed two weeks, it ceased entirely. The treatment was continued for six months, towards the end of which only two doses a day were taken. This patient is 47 years old and now enjoys excellent health."

UTERINE MALIGNANCY—Cancer of the uterus is not amenable to organotherapy, despite several hints that it is. Some cases may seem to respond satisfactorily to such treatment, but it must be remembered that spontaneous cures in carcinoma are not unknown. It is fundamentally wrong to put any confidence in the endocrine therapy of cancer when by so doing we deprive the patient of any radical treatment.

The cachexia resulting from uterine cancer seems to involve the thyroid gland more than does that from malignancy in other parts of the body. A small dose of thyroid once or twice a day is frequently of some symptomatic value. The adrenal cortex hormone has been given in a number of cases of uterine carcinoma with symptomatic benefit to the euphoria, but there was no change in the uterus or the discharge (44).

Several years ago, in a case of advanced uterine cancer with a particularly malodorous exudate, I prescribed 10-gr. doses of mammary substance every three hours, with complete control of the character and odor of the discharge. The family was sure that the old lady was being cured entirely, but it was not so. Theoretically, the depleting effect of mammary substance should make it a reasonable measure in such cases; and, as in the treatment of uterine hemorrhage of less serious origin (80), Mamma-Pituitary Co.* exerts a uterotonic, antihemorrhagic effect in metrorrhagia. The dose is 2 tablets three or four times a day for periods of from ten to fourteen days—it is not taken indefinitely, but periodically.

METRORRHAGIA—Intermenstrual bleeding and uterine hemorrhage after the menopause are serious clinical signs that should cause grave concern. Not all the causes are really serious; among these are hypertrophic endometritis, erosion of the cervix, and uterine polypi, none of which are considered of especially great moment. But it requires a supergynecologist to differentiate some types of cervical erosion and early malignancy.

This is not the place to discuss the differential diagnosis of metrorrhagia, but a simple condition responds to treatment, while a malignant or near-malignant one does not. Three tips are submitted for what good they may do: The treatment is either (1) curettage, (2) decongestive organotherapy, or (3) measures directed at the blood coagulability and the calcium index.

I am undecided about X-ray and radium therapy as a palliative of metrorrhagia. They may be all right in skilled hands as a *radical* measure, where surgery is inadvisable; but many experiences confirm me in opposing X-ray and radium as substitutes for *simple* measures.

Decongestive organotherapy is identical with that outlined in the treatment of menorrhagia (80), and varies with the diagnosis. It will be seen that flooding can occur in hyperthyroidism (due to ovarian irritability) as well as in hypothyroidism (due to uterine infiltration, bogginess, and inelasticity). Obviously, the treatment differs. Again, pelvic hyperemia may be a result of ovarian disease or dysfunction. The former requires radical treatment, while the latter responds to the regulation of the causative upset. As a recent convert to the routine use of organotherapy said, "You can do wonderful things with organotherapy, but you've got to know your stuff." And this "stuff" is rarely learned from books—it is acquired by experience.

The last of the organotherapeutic possibilities in menorrhagia has to do with parathyroid therapy. Occasionally metrorrhagia is exaggerated by defective blood coagulability due to hypocalcemia. In such cases, nothing compares with parathyroid-calcium treatment, and it has the advantage of indicating the correctness of one's presumptions within three or four weeks of its institution. This treatment is a near-specific for chronic ulceration (95).

EROSION OF THE CERVIX—The suggestion is made that cervical erosion be treated as a form of ulceration. In many cases, I have added parathyroid to my therapeutic recommendations, but never advise it alone.

A patient with a recurrent and extensive erosion came to me for advice, and I gave her the usual Para-Spleen Co.* to be taken 1 tablet q.i.d. for two months without a break. She had taken several courses of local treatment, and it happened that she did not or could not take any other treatment. The erosion was healed completely and the discharge stopped. On examining the

cervix, her physician could not believe his eyes. I was asked why this treatment had not been recommended long before. The answer was, of course, that the parathyroid therapy of chronic ulceration is not yet a generally accepted measure, and there are no references whatever to this idea in the recent text-books on gynecology. Yet this treatment is used successfully in burns (42), chronic colonic ulceration and sprue (53), middle-ear disease (54), chronic sinusitis (76), and chronic leg ulcers (95). For the same reason, it is recommended in chronic vaginal and cervical ulcerations.

LEUKORRHEA—Many a case of intractable leukorrhea, which has received local treatment with tamponade, douches, etc., is not satisfactorily controlled until the associated dysovarism and the other results of imbalance in the ovarian trinity—ovaries, thyroid, and pituitary—are regulated by suitable organotherapy (80). In fact, endometritis is often much more than a local endometrial infection and congestive reaction thereto; it may be an indication of the need for endocrine study and treatment.

When dysovarism and leukorrhea are found together, both must be treated simultaneously. The pluriglandular upset causing the dyscrinism will rarely respond directly to the most effective control of the leukorrhea. Likewise, the benefit from indicated treatment of the local, infective, circulatory difficulty will be limited. Local treatment should always be supplemented by the correction of the endocrine background.

UTERINE SUBINVOLUTION following a normal birth is far more common in women who do not nurse their children. It really may be considered to be a penalty that Nature exacts for neglecting this duty. Since the act of nursing, itself, exerts a uterotonic effect, agalactia may be a direct cause of uterine subinvolution. When, for various reasons, nursing is delayed or avoided, something should be done to offset the missing uterotonic stimuli.

Physicians who have discovered the galactagogue value of organotherapy (70) occasionally are loud in their praise of its coincidental involutive effect. So marked is this that, if the involution of the uterus is not proceeding as it should, despite the fact that the baby is nursing well, the galactagogue formula, Placento-Mammary Co.,* may be given in full dose—2, q.i.d. for a month—in the expectation that the uterine effect may be helpful.

The procedure known as pelvic depletion (106) is of value in all types of uterine bogginess, but I do not advise it in postpartum subinvolution until the organotherapy has been used for at least a month or six weeks after delivery; then it is employed in addition to the oral therapy.

97. VIRILISM

Bisexualism—The Endocrine Balance—A Menopausal Manifestation.

THE TERM "virilism" or "virilescence" is, as Dunglison put it, "the state of the aged female in which she assumes some of the characteristics of the male."

BISEXUALISM—One of the strangest things in nature is the fact that many animals, including *homo sapiens* and fowls, are bisexual; that is, in each sex they combine physiological traits of both, which peculiarities are kept in control by the normal balance of the glands of internal secretion. If, however, this equilibrium is upset, a gradual preponderance of the characteristics of the opposite sex may ensue. For instance, it is well known that old hens past the laying age, or sterile birds that never lay, acquire a plumage like that of the male bird; they also try to crow.

Psychologists, in particular, base a number of their conclusions on this balance between the sex features. In his book, "Sex and Character" (London, Wm. Heinemann, 1927, p. 54), Otto Weininger, of Berlin, expresses some interesting ideas that have a bearing on the psychological aspects of this matter. He says:

"The proportion of the male to the female principle in the same human being must not be assumed to be a constant quantity. An important new conclusion must be taken into account, a conclusion that is necessary to the right application of the principle which clears up in a striking fashion earlier psychological work. The fact is that every human being varies or oscillates between the maleness and the femaleness of his constitution. In some cases these oscillations are abnormally large; in other cases, so small as to escape observation. But they are always present, and when they are great they may even reveal themselves in the outward aspects of the body."

THE ENDOCRINE BALANCE—These changes in "the outward aspect" are, it is believed, results of the variation in the regulators of this bisexual balance. For instance, the pituitary dystrophy known usually as Fröhlich's syndrome and the condition of hypogonadism called eunuchoidism cause an upset in the endocrine equilibrium with a lessening of the masculine traits while the feminine ones become quite noticeable. For a further consideration of some of the clinical aspects of this strange manifestation, the reader is directed to the discussions of Hypopituitarism (83) and Eunuchoidism (58).

The adrenal neoplasm known as hypernephroma (35) brings about changes in the endocrine balance, which include a nullification of the essentially sex-regulating influences of the gonads. Every case of virilism must be studied

from this aspect. In hypernephroma, the incidental manifestations of virilism are of small importance compared with the seriousness of the adrenal disease.

A MENOPAUSAL MANIFESTATION—Again, virilism may be essentially a hypofeminism resulting from diminished or lost ovarian functions. This usually occurs in women past the menopause. The symptoms are physical, functional, and temperamental. Mannishness in women may not be an endocrinopathy, but the physical findings of hypertrichosis and of mammary and uterine atrophy certainly are.

Virilism, being usually the result of anatomical degenerative changes rather than functional disorders, is not ordinarily amenable to treatment. The fundamentals of homostimulative organotherapy cannot apply, and substitutive organotherapy does not substitute for that which is lacking.

Probably there is a functional type of virilism, which, if treated early enough, might respond to organotherapy; but persons with this difficulty usually are not concerned about their trouble in time to check it. The treatment should be reactivating and directed at every endocrine factor likely to be involved—adrenals, ovaries, pituitary, and thyroid. The formula, Adreno-Ovarian Co.,* contains these extracts, and is used chiefly in the atonic or asthenic type of dysovarism. Frequently evidences of a restored balance follow such treatment, but some phases such as hypertrichosis (64) are particularly resistant.

V

APPENDIX

98. SUPPLEMENTARY THERAPEUTIC MEASURES

THE READER'S attention has repeatedly been called to the fact that, in the majority of cases in which endocrine therapy is advisable, it is recommended *as a part of the indicated treatment.* Dyscrinism never comes alone. It is always a part of a syndrome, regardless of whether the initial difficulty was solely endocrine or not.

We are never confronted with pure endocrine dysfunction; for, since most endocrine disorders are chronic, they lose their text-book simplicity long before the patient seeks aid from his physician. A gland that is awry corrupts many of its associates, sometimes quite non-glandular associates.

Frequent emphasis also has been given in this volume to the necessity for *treating the patient rather than his disease.* The physician who pays special attention to the endocrines acquires certain therapeutic leanings quite apart from organotherapy. Such associate treatment may be very important. Just as it has been shown that organotherapy may make all the difference between success and failure in a given case, so this supplementary treatment may make much difference in the results from the more specifically endocrine part of the treatment. It may affect that all-important factor, the patient's responsiveness to the needed endocrine stimulation.

Since so much depends upon the endocrine response, this particular point is of extreme importance. Time and again, in the struggle against heavy odds in an old and resistant dyscrinism, the balance has been weighed in the patient's favor by some such simple supplementary measure as hepatic detoxication to spare the endocrines from duties that the liver should be carrying, or remineralization to neutralize the common tendency to acidosis which likewise releases the endocrine glands from duties that they can ill manage.

Just as we agree that it is "the last straw that breaks the camel's back," so we admit that it is the last ounce that turns the scale.

Some physicians have criticized pluriglandular therapy because "one cannot know to which part of the treatment to attribute improvement, if any." The same objection is occasionally raised against combining other measures with the glandular treatment. My best reply to this position is that no self-respecting physician will withhold any indicated procedure just because it may interfere with the accuracy of his clinical conclusions about the efficacy of the rest of the treatment. The most important thing is to help the patient as much as possible and as quickly as possible, for his physical needs surely far transcend the doctor's need for information from his clinical deductions.

Another criticism that has been made, usually with derogatory intent, is that most, if not all, clinical results observed after endocrine therapy—especially oral endocrine therapy—are "purely psychic." This criticism is not quite so condemnatory as might be thought, and its justice may be admitted readily, only with the proviso that the effects are not "purely psychic" but only partially so.

Leaving out of our present consideration the very large class of mentally abnormal patients, it will be conceded that virtually all patients are ill emotionally as well as physically. It is an every-day observation that patients feel better after consultation with the physician, even though they may have received nothing but good advice—neither medicine, nor manipulation, nor instrumentation. Sometimes they comment on it smilingly and conclude erroneously that, after all, they do not need a doctor. This is not the place to enter into this phase of the subject, but I may add a few words about the criticism itself. Assuming for the moment that the effect experienced from the ingestion of endocrine remedies is only psychic, it would still be a beneficial effect—it would help the patient over his distress and would establish a better frame of mind, through which the autonomic nervous system would be given an opportunity to regain its equilibrium. Surely nobody will deny that the working of the sympathetic nervous system is very largely under the domination of emotional factors. To do so would be to ignore all the remarkable and important findings that Walter Cannon, of Harvard University, published as long ago as 1913, and which have been accepted universally.

After all, patients apply to the physician to be relieved of their troubles, and, as has just been remarked, they must be treated for whatever ails them and not with any preconceived idea. They do not care what part of the treatment accomplishes the purpose; they do not even mind whether they are treated scientifically or according to the teachings of some cultism—just so

they are relieved. Still, the fact has been demonstrated time and time again in observations amounting to clinical experiments that certain undeniable changes for the better occurred in patients under the influence of glandular substances taken by mouth, that these beneficial changes ceased when the remedy was omitted, and were reestablished when it was taken again. When these observations are repeated again and again they cease to be coincident, and must be accepted as facts. So much for the reproach that the effects of oral endocrine therapy are psychic.

Physicians who have seen fit to agree with my point of view, repeatedly report benefit greater than they had anticipated, even better than they had come to expect from previous clinical experiences with organotherapy. I do not believe that this change in prognosis can be considered as due to any one cause—either the improved character of the glandular products, the broader (pluriglandular) treatment, the extra detoxication, or the remineralization. The benefit is due to *the larger consideration* that has been given to the patient's problems. This is indeed my excuse for the emphasis given to the minor endocrine phases of many diseases (5) and for the stress I have put on the pluriglandular character of so many endocrine dysfunctions (6).

So, let us do everything we can for our patients, adding to the indicated treatment—endocrine and otherwise—the best supplementary measures that can be used to broaden our service. Then let us not worry about which of these methods should be credited for the benefit that may follow.

99. ALIMENTARY FLUSHING

IN THESE days of colonic irrigations, it may seem superfluous to suggest that, since most chronic disorders have an important intestinal phase, they can be improved considerably by alimentary flushing. Nevertheless, the suggestion is made, although the flushing referred to does not require apparatus of any kind, and costs nothing!

A number of years ago I happened to run across an idea regarding alimentary flushing that has turned out to be real therapeutic gold. That is why it is being outlined here:

It has been found that an isotonic salt solution, normal saline, with a specific gravity about equal to that of the blood, almost always will pass through the stomach and bowels practically unabsorbed, because there is an even balance of the osmotic tension between the blood and tissue juices and this saline solution (approximately two level teaspoonfuls of table salt to one quart of water). Therefore, it can be made to serve as an alimentary flushing procedure of inestimable value—"an enema from above," as it has been called.

Prescribe a full quart of the saline solution (hot or cold—not lukewarm) to be drunk rapidly on an empty stomach. The four glasses—sometimes three will suffice, although four are better—should be disposed of in about five minutes; the flushing effect is lost if the water is sipped slowly. The ideal time to take this treatment is an hour before the usual rising time. After drinking the fluid, the patient should remain in bed, lying on the right side. About an hour later there will be two or three generous liquid stools, and the patient usually remarks about the thorough cleansing character of the draught.

There is only one common contraindication—marked degrees of mucous colitis. Sometimes the bowel may be so irritated that there is considerable pain from the stretching produced by the flushing. In most cases, however, this very stretching is especially desirable, since it unloads fecal material that may have been in the kinks and folds of the bowel for several days, while the feces passed by it.

This flushing procedure is continued for two or three consecutive days, and, depending upon the conditions present, should be repeated occasionally —say, once or twice a week for some time.

Alimentary flushing with normal saline is an unusually effective measure, simple and inexpensive, and not really so inconvenient as it may seem to be at first.

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100. REMINERALIZATION

MY INTEREST in the study of the endocrines was first aroused while doing some research in the urinary acidity (1907-1910). Acidemia, or a reduction in the alkaline reserve with a urinary acidity of from two to four times the normal and an increase in the urinary ammonia (due apparently to incomplete anabolism by the liver of the urea precursors), is frequently associated with indicanuria and reduced urinary solids. This is a common picture in endocrine patients.

The endocrines are vitally responsible for the maintenance of the cellular chemistry. The thyroid presides over the intracellular metabolism; therefore, hypothyroidism produces a tendency to acidosis. The adrenal cortex certainly has to do with the destruction of the muscle poisons, hence the fatigue syndrome is manifested in hypoadrenia—and part of it is due to the accumulation of lactic acid in the muscle cells. In the adiposogenital type of hypopituitarism, the slowed chemistry obviously is responsible for the defective burning of fats and other wastes as well. Hypoinsulinism, or Langerhansian insufficiency, produces the chemical imbalance that causes acetonuria and acidosis of maximum degree.

Hence, acidosis is a customary finding in practically all endocrine difficulties. It is identical with what the French have called *démineralization,* or the robbing of the system of the alkali reserve that is kept available in the tissue juices for the neutralization of acid wastes as they are formed.

The ideal therapy of a condition of this nature is threefold: (1) The fundamental cause should be discovered and controlled; (2) resultant endocrine difficulties that are largely responsible for the clinical picture should be ameliorated by suitable treatment, including proper organotherapy; and (3) remineralization by means of a basic diet and alkalies should be instituted.

Remineralization can be brought about in two ways: (1) by encouraging a better metabolism, and (2) by actual administration of the alkaline mineral salts. Unfortunately, alkaline therapy does not interfere with either of the two common underlying causes—the initial difficulty and the endocrine reaction to that difficulty.

In other words, if our purpose is to treat the patient, and if our attempt is to be as thorough and our service as complete as possible, we must include remineralization, for most endocrine cases require it. Because of this, a mixture of mineral salts in proportions similar to those in which the alkalies are found in the blood-serum, known as Calcium Phosphorus Co.,* is successfully used in conjunction with endocrine preparations. The dose is three 1-Gm. tablets crushed, with much water (two glassfuls are better than one)

an hour before food twice a day for three weeks—thereafter on alternate weeks. In treating children, it may be an advantage to give two tablets once a day, always as far away from meals as possible. In cases of marked acidosis, as in diabetes mellitus, the dose may be increased; but, if more than four tablets are given at one time, there is the probability of saline catharsis. It is extremely important to avoid the neutralization of these alkaline salts in the stomach; hence the timing of the dosage as suggested.

Many a post-operative complication, as well as much of the discomfort following surgery, is due essentially to acidosis. The anesthetic itself and the accumulation of intracellular wastes during anesthesia aggravate the acidosis. For this reason many surgeons now prescribe remineralization as a part of the presurgical routine. This procedure promotes the building of an alkali reserve, which helps to prevent the inevitable toxemia during and after the operation. Prevention is better than cure.

Certain persons lose the faculty of properly appropriating alkalies—lime in particular. Their urinary acidity is high, and the blood calcium is low. Hypocalcemia is especially common in persons who have a long-standing chronic ulceration—tuberculosis, sinus infections, chronic leg ulcers, sprue, or intestinal ulceration. Hypocalcemia is not only a form of demineralization but a defect in the ability to fix or utilize calcium. The parathyroid glands evidently supply what may be called "a calcium mordant," so, in cases of marked lime starvation, Para-Spleen Co.* is a helpful addition (95).

It is admitted frankly that the mineral earths are crystalloid in character and, therefore, not colloid or "humanized," and that the body promptly attempts to eliminate them as completely as possible. It is also admitted that the majority (94 per cent., according to H. A. Salvesen, of the University of Oslo) of the calcium salts given by mouth, rectum, or by intravenous injection, are eliminated within forty-eight hours, chiefly in the feces in the form of calcium sulphide. During that short time, however, a large proportion of these minerals has come in contact with various acid wastes and promptly neutralized them. Even though these minerals cannot be stored up in their present form by chemical processes alone, they neutralize acid wastes effectively and thereby spare the acceptable colloidal minerals that are found in the food and permit them to be utilized and built into a reserve. Any clinician who has given ordinary non-colloidal mineral salts knows how great is their neutralizing and restorative value in suitable cases.

In conclusion it may be said that remineralization is the handmaiden of organotherapy. Many a failure from the use of active endocrine products in suitable cases is turned into success by associating with it this simple and ordinary therapeutic measure.

101. THE VITAMINS

ONE WRITER has aptly called the vitamins "food hormones"—factors necessary to the nutritional responses. The definition given in the dictionary, however, is more comprehensive: "A nitrogenous substance found in some nucleic acids, minute quantities of which are essential to the diet of man as a nutritive force and for stimulating growth." Then, too, Dorland refers to "auxohormone" as a term applied to vitamins, which shows that others have connected the vitamins and the internal secretions.

Certain endocrinopathies are essentially disorders of nutrition, so, when confronted with a serious and fundamental disorder of this nature, if there is more than one way to influence the underlying factors, obviously all methods should be utilized. Consequently, many an endocrinologist has been interested in the vitamins; in fact, it was an endocrinologist who used the apt term, "food hormones," mentioned above.

The more we learn of these subtle substances and the more research that is done with them, the more convincing become the evidences of their close association with the endocrine functions. This is true of vitamin *A* in the immunizing response to infections, of vitamin *D* in its relation to the calcium metabolism and in other cases in which parathyroid therapy has proved so spectacularly helpful. The antisterility vitamin *E* seems to exert its specific effect solely on an essentially endocrine function. So, not only for the sake of completeness, but because there is a very definite connection between vitamin and endocrine therapy, a brief consideration is given here to these accessory food principles, chiefly from the standpoint of therapeutic agents supplementary to the treatment of dyscrinism.

VITAMIN *A*—THE "ANTI-INFECTIVE" FACTOR: There are two obvious effects attributable to a deficiency of the fat-soluble factor in the diet: failure to grow (in the case of young rats) and ophthalmia. Apparently, however, xerophthalmia is not due directly to the absence of vitamin *A*, but is an infection that is able to exist because a lack of vitamin *A* produces a general susceptibility to infections. During an African expedition in 1857, David Livingstone noted the appearance of xerophthalmia produced by a scarcity of butter and other animal fats. Lack of vitamin *A* has been said to cause night-blindness, which has been treated with liver extract—a good source of vitamin *A*.

Because of the susceptibility to infection caused by a lack of vitamin *A*, Green and Mellanby suggested that this vitamin be named "anti-infective." In fact, the beneficial effects that they observed in animals led them to

administer products containing vitamin *A* to patients suffering from puerperal septicemia.

Some interesting work has been done in the treatment of pernicious anemia with vitamin *A* as well as with liver extract. While Minot and Murphy were treating pernicious anemia patients at Harvard Medical School by feeding them liver and liver extract, Koessler and his associates in Chicago were treating this disease with vitamin *A*. They explained that pernicious anemia was due to an absorption from the intestine of toxic substances produced by bacteria. Best and McHenry, however, recently called attention to the fact that Cohn and others had alleviated pernicious anemia with fractions of liver extract containing no vitamin *A*.

The structural alterations in the endocrine glands caused by vitamin-*A* starvation are astonishing. There is a decided hypertrophy of the adrenals, but an atrophy of the thymus, the parathyroids, and other glands. The parathyroids are rendered susceptible to injury by bacterial and toxic agents. A lack of this vitamin lowers intestinal motility and causes degenerative changes that render the intestinal wall more permeable.

Vitamin *A* withstands heat remarkably well in the absence of air, and foods heated in air lose this vitamin rapidly because oxidation is accelerated by heat. The best sources of vitamin *A* are the fats of animal origin, milk, butter, and cod-liver oil. It is not found in vegetable fats, but is present in large quantities in green leaves and in actively growing portions of plants.

VITAMIN *B*—THE ANTINEURITIC, GROWTH-STIMULATING FACTOR: Vitamin *B* is a nitrogenous substance essential to nutrition, antineuritic in character, and stimulating to growth.

The first experimentally produced deficiency disease was caused by feeding a diet lacking in vitamin *B*. In 1911, Casimir Funk isolated from the coating of rice grains a concentrated fraction that would cure experimentally produced polyneuritis. He named this factor "vitamine" because it appeared to be a nitrogenous base of amine character, essential to life. McCollum and Davis (1915) demonstrated the necessity of a water-soluble factor for the growth of rats. This seemed to be identical with the antineuritic vitamin, and it was called "water-soluble *B*." Two effects—antineuritic and growth-promoting—were attributed to it. The two factors that stood out particularly in the work of Goldberger, however, were the antineuritic factor and a pellagra-preventing factor. For a time these particular two were designated as B_1 and B_2. In 1929, McCollum and Simmonds suggested that the pellagra-preventing factor be designated as vitamin *G*, in honor of Goldberger. This terminology has been quite generally adopted.

A marked deficiency of vitamin *B* produces beriberi, the results being fatal in a short time. In the early stages, however, a cure is easily brought about by proper feeding.

My work with the growth-stimulating substances, especially the fraction from the anterior pituitary containing the growth hormone, has run parallel with certain studies of the growth-stimulating influences of the vitamins. After several months of clinical experience, I decided to supplement the endocrine principles with a suitable dose of vitamin *B*, with the result that this product, Accretin,* is still more potent as a growth stimulant.

The effect that vitamin-*B* starvation produces on growth is more easily understood when one studies the pathological changes that are wrought in the endocrines. These changes are similar to those caused by vitamin-*A* starvation, *i.e.*, hypertrophy of the adrenals and the pituitary, but atrophy of the other glands—especially the thyroid and the sex glands. The latter become atrophied in both the male and the female. The glands, then, that play such an important part in growth—the pituitary, the thyroid, and the gonads—are definitely altered by vitamin-*B* starvation.

In this connection it is interesting to note that during the Great War there was a decided increase of amenorrhea and sterility in women of child-bearing age—due, it is believed, to vitamin deficiency. Vedder states that women suffering from beriberi cease to menstruate. In 1921 Evans and Bishop demonstrated that the ovulation rhythm is an especially sensitive indicator of deficiency in vitamin *B*.

As vitamin *B* is soluble in water, much of it is lost when the water used in cooking is thrown away; and the longer food is cooked, the more this factor is destroyed. Fortunately, there are many sources of vitamin *B:* eggs, peas, beans, whole grain, asparagus, spinach, tomatoes (raw, cooked, canned, or dried), wheat embryo, yeast, meats, kidney, liver, cabbage, carrots, cauliflower, lettuce, milk (depending on the cow's diet), etc.

VITAMIN *C*—THE ANTISCORBUTIC FACTOR: Progress in the investigation of scurvy was slow until it was discovered that the experiment animals develop that disease when placed on certain diets. In 1895, Theobald Smith observed the development of scurvy in guinea-pigs limited to a diet of oats and bran.

In addition to this antiscorbutic property, vitamin *C* apparently has important functions in maintaining the resistance of the body to various infectious diseases. Sherman even suggests that much of the so-called "rheumatism" that afflicts a large proportion of people in late winter and early spring may be due, at least in part, to diets low in vitamin *C*.

The adrenals are the principal glands concerned with vitamin *C*. Sajous has emphasized this relationship and has even suggested that the adrenals are a source of vitamin *C* and that this substance is the paramount factor of tissue life, the agent which, as a component of hemoglobin in the red corpuscles, furnishes oxygen to all tissues.

It was Sajous' well-known "all science" method that enabled him to discover the identity of the water-soluble antiscorbutic vitamin *C*, which in foods he found to be the oxidizing ferment tyrosinase. Sajous has produced evidence showing that tyrosine is the homologue of adrenin. Years ago he showed that the adrenal principle was, or included, an oxidizing ferment, which he called "adrenoxidase." Chemists had shown that tyrosine possesses a similar ferment. "If the tyrosine of foods is homologous to adrenin," remarked the editor of *American Medicine* some time ago, "and the latter sustains tissue oxidation as vitamin *C*, we have, in foods containing this vitamin, potent agents for the preservation of health in the multitudes of people who, though not actually ill, show abundant evidence of 'low vitality.' "

When a diet is deficient in vitamin *C* alone, the enlarged adrenals are associated with diminished adrenin content and hemorrhages. McCarrison found that this condition of adrenal function occurs before there are clinical manifestations of scurvy.

Vitamin *C* is destroyed by fairly mild oxidizing agents. It is also readily inactivated by heat, and alkalinity is very destructive to it. Under appropriate conditions, canning does not destroy the antiscorbutic activity. Canned tomatoes are usually very rich in vitamin *C*. The best sources of this vitamin are: tomato juice, orange juice, lemon juice, fresh vegetables, and milk from cows feeding on fresh green food.

VITAMIN *D*—THE ANTIRACHITIC FACTOR: It was in 1919 that Huldschinsky reported that ultra-violet radiation cured rickets in four children. Previously (1918) Mellanby had found that cod-liver oil would prevent rickets in dogs. A little later, Sherman at Columbia University, and McCollum at Johns Hopkins, discovered that a proper supply of calcium and phosphorus was necessary to prevent rickets.

This produced a dilemma: Cod-liver oil, known to be rich in vitamin *A*, cured rickets, but other substances rich in this vitamin did not have a marked curative effect. Furthermore, calcium and phosphorus were necessary to prevent rickets. The matter was clarified in 1922 when McCollum and his associates proved that cod-liver oil contains not only vitamin *A* but also another vitamin which, in addition to calcium and phosphorus, is essential

to proper bone formation. This new factor was called vitamin *D*, or the antirachitic vitamin.

These two factors apparently belong to a class of compounds known to chemists as sterols. Ergosterol appears to be the mother substance of vitamin *D*. After a brief period of radiation, ergosterol becomes extremely potent and possesses 100,000 times the antirachitic activity of the same weight of the strongest cod-liver oil.

There has been a great deal of ballyhoo about vitamin *D*—Viosterol, cod-liver oil tablets, and innumerable other products containing this principle. The pendulum has swung very far, and now, as is usually the case, the reaction is beginning. For instance, experiments are reported from the University of Tennessee (*Drug Markets,* Feb., 1930, xxviii, p. 137) showing that animals fed on a purified diet adequate in proteins, inorganic salts, calories, and vitamin *B* grow well for a short time, then the weight becomes stationary or falls off rapidly, and xerophthalmia and intestinal disorders develop. The addition of irradiated ergosterol to a diet like this increases the calcification of the bones but does not prevent or cure the xerophthalmia nor increase the growth of the animals. Most of the symptoms are as bad as, if not worse than, the conditions found when no irradiated ergosterol is given. The addition of cod-liver oil to the original diet, however, results in excellent growth, a better calcification of the bones, increased deposition of body fat, and freedom from the intestinal disorders accompanying other diets.

Blunt and Cowan report that cod-liver oil probably exerts its effect on calcium metabolism by stimulating the parathyroid tissue to increased activity. Proof of this is also found in the experiments of Greenwald and Gross.

Several of the calcium studies by workers with vitamin *D* and with the parathyroids show a parallelism. Parathyroid therapy fixes lime. So apparently does vitamin *D*. The latter is beneficial in conditions in which parathyroid is specific, *e.g.,* chorea, spasmophilia, tetany, etc. The ultra-violet ray is valuable in parathyroid dystrophies just as it is in the disorders in which vitamin *D* is so spectacularly helpful. These findings and a number of others confirm the suspicion that the capacity of the organism to appropriate lime and the corresponding capacity to heal ulceration and neutralize certain types of toxemia (by means of the increase in the tissue lime) are subject to the influences of the parathyroids, vitamin *D,* and sunlight—real or artificial. Naturally, then, whenever there is a problem to be solved, it will be helpful to use all three of these facilities. It is undoubted that each supplements the other in decisive fashion.

The sources of vitamin *D* are limited, cod-liver oil and certain fish oils being the only natural materials particularly rich in it. Ergosterol, as has

been mentioned, is very rich in vitamin *D*, and sunlight and ultra-violet light are good rachitis preventives.

VITAMIN *E*—THE ANTISTERILITY FACTOR: In 1922, Evans and his associates at the University of California found that rats raised on diets of synthetic materials containing ample amounts of vitamins *A* and *B*, lived and grew normally, but became sterile. The sterility eventually was proved to be due to the absence of a dietary factor, and could be prevented or cured by certain foods. This factor was called "the fat-soluble antisterility vitamin *E*."

A diet deficient in vitamin *E* affects males and females differently. In the male there is destruction of the germ cells and eventually of the entire seminiferous epithelium. In the female, however, the ovary and ovulation are unimpaired throughout the sexual life. A disturbance occurs, however, at gestation—there is death and resorption of the developing young.

Vogt remarks that "the antisterility vitamin *E* and the ovarian hormone must be closely related, for their activities are extensively dependent upon each other." It should be noted that the sterility resulting from vitamin-*E* deficiency is a peculiar type. Sterility, particularly of the male, may frequently occur as a consequence of a lack of other vitamins, but their lack will not cause the same conditions that are produced by an insufficient amount of *E*.

In 1924 and 1925 Evans and Burr so concentrated vitamin *E* that 5 mg. of the final yellow viscous oil saves a pregnancy that would result in death of young at midgestation.

When the male sex hormone was in process of perfection it was suggested that vitamin *E* might sensitize the experiment animals and birds more thoroughly to its effect (11). The results were very satisfactory. Since Lydin* has been made clinically available, 20 per cent. of vitamin *E* has been combined with it.

Vitamin *E* seems to be the most stable of the vitamins, being resistant to heat, mild oxidation, and chemical treatment. It is intimately associated with the fats and hence is said to be fat-soluble, but it is not a sterol.

Vegetable materials, particularly green leaves and seed germs, are rich sources of vitamin *E*.

VITAMIN *F*—THE ANTIBERIBERI FACTOR (also known as B_1): Sherman has proposed that the antineuritic or antiberiberi factor of vitamin *B* be called vitamin *F*.

VITAMIN *G*—THE ANTIPELLAGRA FACTOR (also known as B_2): See vitamin *B*, page 658.

102. DIETETIC CONSIDERATIONS†

SEVERAL ESSENTIALLY endocrine disorders are of such a nature that organotherapy alone must fall short in certain respects, despite its potential efficacy. Since the food we eat has much to do with the service our organs are capable of performing, dietetics is a very necessary handmaiden of endocrinology. No intelligent physician would think of treating diabetes without organotherapy and dietetics; many gastro-enterologists no longer expect to treat colitis with dietetics without organotherapy; and so on.

So it seems advisable to outline briefly the essence of the dietetic control of certain endocrine disorders that can be treated much more successfully by this method associated with the indicated organotherapy.

Anemia—In the treatment of secondary anemia, R. S. Reeves, of Philadelphia (*Am. Med.*, Aug., 1929, xxxv, p. 534), suggests that, after removing the cause, a diet that will restore blood to normal should be used. At least a quart of milk a day, with eggs, cereal, bread, toast, cream, preserved fruits, and vegetables, is as necessary, in his opinion, as are liver, kidney, and raisins. But, in prescribing a high caloric diet, vitamins and minerals must not be overlooked.

In "Practical Dietetics in Health and Disease" (Philadelphia, F. A. Davis Company, 1928, p. 2), Sanford Blum, of San Francisco, prescribes diets for young and old in various occupations, but recommends the following as a general dietary for mild anemia that has been brought about by improper diet:

Breakfast 8 A. M.: A glass of milk or cocoa; a bowl of cereal; two slices of bread or toast, and butter; fruit.
Luncheon 12 M.: Meat, vegetables, bread and butter, plain pudding.
3:15 P. M.: Glass of milk.
Supper 6 P. M.: Light meat, vegetables, salad, bread and butter, dessert.

His patients are advised to drink water freely between meals; to eat simply prepared, plain, nutritious food, at regular times; and to avoid sauces, condiments, and gravies.

Richard M. Field,† of Jamaica, New York, advises such patients to avoid pork, ham, veal, shell-fish, salmon, shad, mashed or fried potatoes, sweets—especially at meals—coarse, heavy vegetables, skimmed milk, tea or coffee at meals, fresh or white bread, also too great a variety at one meal.

Blum advises the same dietary in pernicious anemia as in secondary anemia,

†NOTE: For the convenience of general practitioners, Dr. Richard M. Field, of Jamaica, New York (P. O. Box 168), has perfected a series of printed dietetic instruction sheets for the direction of this phase of the treatment of many disorders. It is suggested that the reader should obtain them.

except that liberal portions of visceral substances instead of other meats should be provided. He prescribes from one-fourth pound to one pound of liver daily, either raw or cooked, for indefinite periods. It may be served in cocktail, timbale, cooked in soup, sauté'd, broiled with bacon, boiled, scrambled or fried with eggs, as liver sausage, and in various other forms. Sweetbreads, brains, kidneys, lungs, or heart may be substituted for liver for those who can eat them.

A diet that is of high protein value and low in fat content—largely in the form of calves' liver—is suggested by Minot and Murphy. The daily portions suggested are 200 Gm. or more (cooked weight) of freshly cooked liver; about 400 Gm. of fruits; 125 Gm. or more of red-muscle meat trimmed free of fat; not less than 300 Gm. of vegetables containing from 1 to 10 per cent. of carbohydrates; not more than 70 Gm. of fats, very little cream and butter, and only one egg; avoid grossly sweet foods; use sugar sparingly; add starchy foods to suit individual desires, but not to exclusion of requirements given above—starchy foods must be crusty or dextrinated—milk should be limited to 240 Gm.; avoid excess of salt; give tea and coffee as desired.

However, the liver *diet* in the treatment of pernicious anemia is now superseded by liver *therapy* (40).

Mucous Colitis—It is generally conceded among gastro-enterologists that some fats seem to be more beneficial in mucous colitis than others. In order of importance, they are: dairy fats, olive-oil, and mutton fat. This same order seems to hold good in ulcer cases also.

The high-fat, low-residue diet is most important, and until the patient is better he should take no vegetables, protecting himself in the matter of vitamins by using plenty of milk and the water poured off the vegetables—"vegetable consommé," as it has been called. When improvement is noticed and the gas and distress are less, he should start taking soft vegetables thoroughly puréed, such as baked potato, Hubbard squash, some of the soft fruits such as bananas (baked) and avocados, and the citrus fruit juices.

After the patient has started taking vegetables, he seldom can continue them regularly. There will be times when he will have to discontinue them entirely, taking starchy foods that are soft, and that contain a minimum of residue. Then, when he is relieved he may again try vegetables for a time. As the bowel heals, its tolerance for bulk gradually returns so that after from eighteen months to two years of careful effort the patient will be able to use—but always very carefully—a fairly normal diet. Here is a typical day's dietary as suggested by Sanford Blum (*ibid.*, p. 42):

Breakfast: Coffee; toast and butter; eggs.
Dinner: Scraped meat, chicken, fish or oysters; stale bread and butter; rice with salt and butter.
Supper: Beef juice; stale bread and butter; baked potato; cup of tea.

Blum suggests that a cup of broth or tea should be drunk in the middle of the afternoon and that water should be taken freely between meals.

Diabetes—There is no ideal diet suited to all diabetic patients, but one must consider the body weight, the diet, and the patient's tolerance. There are those who advocate a high-carbohydrate diet, a low-carbohydrate diet, and a low-carbohydrate, low-protein, and high-fat diet. Newburgh and Marsh, who report good results with the last-mentioned method, say:

"When a patient enters the clinic, he is placed on a diet containing from 900 to 1000 calories, of which about 90 Gm. is fat, 10 Gm. is protein, and 14 Gm. is carbohydrate. After the patient has been sugar-free for one or two weeks, his diet is increased to about 1400 calories, of which 140 Gm. is fat, 28 Gm. is protein, and from 15 to 20 Gm. is carbohydrate. In the case of small individuals, this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1800 calories, containing 170 Gm. of fat, from 30 to 40 Gm. of protein, and from 25 to 30 Gm. of carbohydrate."

As to the advantages of a high-carbohydrate diet, E. P. Joslin, of Boston ("The Treatment of Diabetes Mellitus," Philadelphia, Lea & Febiger, 1928, p. 590), has this to say:

"A common diet in diabetes is carbohydrate 1 Gm., protein 1 Gm., and fat 2.5 Gm., or 30 calories per kilogram of body weight, but I think a better diet would be carbohydrate 1.5 Gm., protein 1.25 Gm., and fat 2.0 Gm., 29 calories per kilogram of body weight."

A still higher carbohydrate diet is advised by Sansum, Gray, and Bowden ("The Treatment of Diabetes Mellitus with Higher Carbohydrate Diets," New York, Harper & Brothers, 1929, p. 3), who allow diabetics 200 Gm. of carbohydrates at the start. They say:

"These diets are high in carbohydrate content and low in fat when compared with former diabetic standards, but they are no higher in carbohydrate or lower in fat than are the accepted standards for normal people. . . . On these diets practically all patients have felt physically stronger and mentally more alert."

The method of treatment followed by Joslin is succinctly stated thus:

"One asks the patient to eat less food, particularly less sugar and starch, and simultaneously prescribes a few units of insulin to offset the loss of his own. Until the urine becomes free from sugar, the total diet is curtailed and the insulin raised. The protein is always maintained at a moderate level or

reduced one-third or even more in the presence of acidosis. The fat is increased to make up for the calories eliminated as carbohydrate, but the total food value of the diet is held 10 per cent. below the normal level unless sugar-free and losing weight. Ultimately the carbohydrate should be about 100 Gm., the protein 60 Gm., and the fat 125 Gm. for the average individual whose naked weight is 60 kilograms. Meanwhile insulin may need reduction or increase and 5 or 10 or 15 units will be injected once, twice, or three times a day. With time, adjustments of diet and insulin may be made and the faithful patient can look forward to an increase in his carbohydrate."

It all depends upon the patient. Just as no hard and fast dosage rules apply in medicine, so it is with the dosage of food. We must feel our way.

There is a valuable algebraic method for determining a maintenance diet, calculated from the patient's weight, but space does not permit its inclusion here. Neither is there space to include a table of fundamental food values, with which every patient who makes up his own menus should be provided. However, I am listing here a few daily menus, which are compiled from diets suggested by a number of authors:

SUNDAY

(A Green or Vegetable Day—Semistarvation)

Breakfast: One egg; cup of black coffee.
Luncheon: Spinach; fish; salad; charged water.
Dinner: One egg; cabbage, cauliflower, or asparagus.
Bedtime: Beef tea or chicken broth.

MONDAY

Breakfast: Van Houten's cocoa and cream; eggs; vegetable salad—cooked or raw.
Luncheon: Lamb cutlets; salad of green vegetables; diabetic flour biscuits with cheese;† lemonade (saccharine).
Dinner: Boiled fish with butter and lemon; veal cutlets; Brussels sprouts; lemonade (saccharine).

TUESDAY

Breakfast: Grapefruit; two eggs; cakes of special flour;† butter.
Luncheon: Fish; asparagus; carrots; diabetic biscuits;† butter or cream.
Dinner: Eggplant; spinach; raw tomatoes; diabetic bread; butter or cream.

WEDNESDAY

Breakfast: One or two eggs; watercress; raw tomatoes; butter.
Luncheon: Broth; steak; string-beans; celery; cauliflower.
Dinner: Broth; eggs; fish; lettuce; tea; butter.

THURSDAY

Breakfast: Orange (in mild cases); fish; one or two eggs; carrots; butter or cream; coffee.

Note: The items marked (†) are specially prepared—no sugar, flour, etc.

Luncheon: Steak; cauliflower; potato (size of egg); butter or cream; tea.
Dinner: Egg; onions; coffee jelly (1 tbsp. coffee, ½ gr. saccharine, three whole walnut meats); small orange; butter or cream; tea.

FRIDAY

Breakfast: Coffee and cream; eggs; Brussels sprouts; celery salad.
Luncheon: Salmon (boiled) with cucumber and vinegar; sirloin beef; asparagus; cocoanut cream.†
Dinner: Cold salmon and mayonnaise;† cold beef and tomatoes; cauliflower; lemon sponge;† aerated water.

SATURDAY

(May be used as starvation day)

Breakfast: One-half apple; fish; eggs; asparagus; coffee; cream or butter.
Luncheon: Lamb chop; peas; radishes; tea; cream or butter.
Dinner: Cold tongue; eggs; tomatoes; olives; grapefruit; butter or cream; tea.

Epilepsy—There are several different dietary methods used in the treatment of epilepsy. Among these are the starvation method, the low protein diet, and the ketogenic diet. Most of the suggestions pertain to taboos and restrictions rather than to additions to a regular dietary.

Regarding the starvation diet, Geyelin has observed that fasting will relieve epileptic attacks once, but not subsequently in the same patient. He says that at the end of the year's treatment we should study our percentage of arrested cases by this method.

Alcohol in every form is prohibited most emphatically by many authors.

Holmes has found that in certain cases a meat-free diet is of benefit, but his experience shows that very few cases profit much by the exclusion of meat, although the amount taken can often be reduced with benefit. The diet should be simple, says Holmes, and overloading of the stomach, and constipation, should be avoided.

Field, however, emphatically opposes the use of all meat except lamb and white chicken, suggesting that fish, eggs, cereals, vegetables, whole-wheat bread, and milk may be substituted for it. In addition to meat, he taboos salt, salted foods; condiments; smoked, pickled, spiced, dried foods; appetizers; melons, unripe bananas, pears; hot breads, white breads; coffee or strong tea; sour foods; sweets, especially with meals; rich desserts. He particularly warns his patients against overeating.

Among those foods that epileptics may safely use, he lists: fresh pea soup or bean soup; baked potato, boiled rice, macaroni, spaghetti with butter

sauce; well-cooked cereals, sweetened with honey; junkets, custards, jello, rice pudding; lettuce or romaine; young carrots or turnips, green corn, spinach, summer squash, cauliflower, fresh green peas or lima beans, lentils, string-beans, celery, fresh tomatoes; fresh fruits, except those mentioned; whole-wheat, corn, brown, or rye bread; prunes, figs, or apples, stewed without sugar; buttermilk, cultured milk; dry cereals.

E. B. McCready, of Pittsburgh (*Med. Jour. and Rec.,* Oct. 16, 1929, cxxx, p. 436), believes that the good results attributed to various diets probably owe whatever efficacy they possess to the incidental elimination from the diet of foods to which the patient may be allergic.

Hypertension—Konikow and Smith prescribe a salt-free diet for hypertension, and their menus include eggs, meat, pepper, spices, vinegar, and vanilla. Rommel, however, reports permanent benefit in cases of hypertension by excluding meat and eggs from the diet as an essential part of the treatment. He says:

"Ten years ago I reduced the blood-pressure of a middle-aged, portly man weighing 260 pounds, by taking all the meat and eggs from his diet. . . . I put him on a strictly milk and vegetable diet. Within three months his blood-pressure dropped to 150 and remained there."

In the treatment of hypertension with obesity, O'Hare restricts the diet as a means of reducing the weight. He advises small meals at all times, to avoid strain on the heart and circulation, restricting protein to 1 Gm. per kilo, salt to what is naturally in the food, and fluids to approximately three or four pints daily.

The day's menu given below is an example of a well-balanced dietary that will aid in bringing down the blood-pressure:

Breakfast: Baked apple with cream; one piece of toast; marmalade; butter; orange juice; coffee.
Dinner: Cream soup; stuffed baked potato; beets in cream; combination salad; one slice bread; butter; olives; pineapple; Bavarian cream.
Supper: Escalloped potatoes buttered peas and carrots; fruit salad; one slice bread; cocoa; nut ice-cream.
Mid-Meal Diets: 10 A.M.—buttermilk; 3 P.M.—fruit juice; 9 P.M.—hot milk.
Foods for Substitution: Almonds, asparagus, beans (lima, dried), cabbage, pears, cauliflower, chestnuts, apples, bananas, lettuce, muskmelons, peaches, potatoes, raisins, currants, lemons, cow's milk, oranges, carrots, radishes, turnips.

Obesity—Although some authors stoutly maintain that all cases of obesity are constitutional, undoubtedly in many cases diet always will be one of the important measures in the treatment. Justice cannot be done to the subject

here, but some of the standard reducing methods will be set down briefly. We might mention first, though, an interesting digression from the usual dietaries:

Instead of cautiously reducing the diets to 14 or 15 calories per kilogram with resulting weight losses of from 6 to 8 pounds (2.7 to 3.6 kg.) a month, Evans and Strang gave their patients half as many calories—from 6 to 8 per kilogram—and obtained a more rapid reduction in weight.

In a symposium on obesity, Rowe said of the dietary treatment:

"A low caloric diet of from 600 to 1000 calories will often bring about the desired reduction in weight. Such diets should contain liberal amounts of fruits and vegetables of the 3 to 5 per cent. carbohydrate groups and moderate amounts of the 10 per cent. groups. Skimmed milk, lean meat, or fish should be taken in moderation at each meal. Fat should be excluded. The diet should contain approximately the following amounts of food, though weighing is unnecessary: carbohydrate, from 50 to 100 Gm.; protein, from 45 to 60 Gm.; fat, from 10 to 20 Gm. Such a diet will contain sufficient carbohydrate to prevent acidosis, enough animal protein for metabolic requirement, low calories, and enough vitamins and mineral salts to prevent deficiency diseases. When reduction in weight occurs the diet can be gradually increased, especially in the carbohydrates and milk, in order to maintain the vitamin and mineral-salt intake."

Sansum's suggestions were practically the same except that the lowest number of calories called for by his schedule is 820 as compared with the 600 suggested by Rowe.

In "Practical Dietetics in Health and Disease" (Philadelphia, F. A. Davis Company, 1928, p. 198), Sanford Blum says:

"There is a limit below which it is inadvisable to reduce the diet. In calculating the amount of food to be prescribed in a dietary for obesity, not the bulk is significant, but the nutritive and heat-producing—the caloric—value. And just at this point may be noted an insuperable obstacle to the routine formulation of exact dietaries suitable to all cases. It is this—that not the amount of food ingested, but the amount metabolized, is important; and it is impossible to know in advance the ultimate fate of food consumed by an individual. The metabolic powers of the individual as well as the digestibility and caloric value of the food will determine the results."

The diet is modified by Blum according to the person's age, weight, occupation, etc.; *e.g.*, he allows a man two soft-boiled eggs for breakfast instead of one; adds a cup of bouillon to the luncheon menu, but allows only one slice of bread and butter instead of two; and adds a small cup of black coffee to the dinner. In the case of a 260-pound woman, he allows only fruit or tea at luncheon. The menu that he advises for an unoccupied woman past

forty, who wishes to retain her youthful figure, is more meager than the average. It is as follows:

Breakfast: Only fruit and coffee or tea.

Luncheon: Cold meat, light meat, fish, or eggs; salad; toast; fruit.

Dinner: Meat, poultry, fish, or eggs; green vegetables; dry toast; salad; fruit; small cup of coffee.

An average reducing diet consisting of 1000 calories is, of course, planned somewhat differently by different physicians, but the following apportionment of calories and choice of foods has been found of exceptional value in reducing weight and maintaining the well-being of the patient:

FOUNDATION MENU

		Calories
Breakfast:	1 helping fruit (see fruit list)	100
	1 thin slice toast	72
	½ square butter (1 level teaspoonful)	36
	1 egg	70
	Coffee or substitute	
Dinner:	Meat or fish, small helping (1/5 lb.)	150
	2 helpings 5 per cent. vegetables (see list)	32
	1 helping 10 per cent. vegetables (see list)	32
	½ square butter	36
	1 glass skimmed milk or buttermilk	80
	1 thin slice of bread	72
	1 helping of fruit	100
Supper:	1 egg or substitute (see list)	70
	2 helpings 5 per cent. vegetables	32
	1 helping 10 per cent. vegetables	32
	1 glass skimmed milk or buttermilk	80
	Total	994

The patient is directed to make his own menus for each day by selecting the fruits and vegetables desired. The diet also can be varied by substituting other foods in the following list for the eggs.

5 per cent. Vegetables

One helping is approximately three tablespoonfuls

Asparagus	Celery	Kale	Rhubarb
Beet greens	Chard	Kohlrabi	Sauerkraut
Brussels sprouts	Cucumber	Leeks	Spinach
Cabbage	Eggplant	Lettuce	String-beans
Cauliflower	Endive	Mushrooms	Tomatoes
	Green pepper	Radishes	

10 per cent. Vegetables

One helping is approximately three tablespoonfuls

Beets	Okra	Pumpkin	Squash
Carrots	Onions	Rutabagas	Turnips

Fruit List

A serving should consist of the amount listed

2 small oranges	2 small peaches	½ medium cantaloupe
1 grapefruit	1 banana	12 to 15 cherries
1 apple	3 or 4 apricots	4 small dates
25 to 30 grapes	1 large pear	3 fresh figs
¼ cup raisins		6 medium prunes

2/3 cup berries and 1 tsp. sugar.

Substitutes for an Egg

1-inch cube American cheese	2 Brazil nuts
4 x 4 x ⅛-inch slice Swiss cheese	12 pecans
2 rounding tbsp. cottage cheese	7 half walnuts
1/3 pkg. cream cheese	25 shelled peanuts
12 or 15 almonds	1 ounce lean meat—1 rounding tbsp.

1 glass buttermilk or skim milk

Tuberculosis—Diet for the tuberculous patient consists of "a sufficient supply of adequate food," says Pottenger. This is the gist of the advice that most specialists give.

In "Lessons on Tuberculosis and Consumption" (New York, Funk & Wagnalls Co., 1922, pp. 222-255), Atkinson advises a dietary somewhat larger than that used by healthy persons—a diet that contains all the food elements in suitable proportions. But he warns:

"Eat the least amount that will produce satisfactory results. Eat foods that count. Improvement is not always accompanied by a gain in weight; but this is not the primary object for which one should strive . . . only so far as weight acquired means a gain in energy and *lung-repair* is it of value."

On the other hand, he says that one cannot "starve the fever" indefinitely without at the same time starving the patient beyond hope of recuperation. If the food does not disagree, the ration should be generous, but the food should be easily digestible. He also advises against attempting to live on milk alone except under unusual and special circumstances. On the "stuffing evil," he is most emphatic:

"Do not exchange perhaps your only chance of complete restoration to health solely for a gain in weight—a mere improvement in appearance, which may but mask the progress of your malady until it is too late. . . .

"When it appears profitable to force the diet, the taking of an extra glass of milk or two, or its equivalent, and one or two raw eggs—between meals—

and perhaps also a similar lunch at bedtime, is a convenient way of accomplishing the purpose. One glass of milk and one egg for the lunches will be sufficient in most cases. The bedtime lunch should be omitted in all but the most stubborn."

This author divides foods roughly into three groups: repair and body-building foods; fuel foods; and reserve foods. As to the food ratio, he says:

"The average *well* person will have the best chance of retaining his health if his meals are arranged so that roughly from one-tenth to one-fifth of his daily ration consists of body-building foods, the menu being completed by the addition of members of the two other principal food groups, preferably combined in such a manner that the *fuel* group is represented in approximately twice the amount of the *reserve* elements. On the other hand, as already intimated, the dictates of reason would lead one to presume that the *sick* person has need of additional food to repair the damage done by disease; as a matter of fact, experience has demonstrated that the sufferer from tuberculosis often can increase, with benefit, his allowance of both the body-building and the reserve foods from 25 to 50 per cent. above the quantity required in health.

"If each individual will fix in mind the relative amount of each food group that is required, and select from each group such foods as agree with him, he will find that the knack of eating to win is easily acquired."

Under body-building materials, Atkinson gives a list of proteins, such as lean meat, fish, milk and milk products, eggs, etc.; under quick fuel materials, the starches and sugars, such as cereals, cereal products, potatoes, and corn; and under reserve fuel materials, the fats and oils, such as meat (fatty part), butter, oleomargarine, cream, yolks of eggs, olive-oil, nuts, etc.

103. IODINE THERAPY

IODINE IS preeminently an endocrine stimulant. It is, indeed, a vital mineral food, and, since the thyroid gland is the only structure in the body containing this element in appreciable amounts, it is dependent upon a modicum of iodine in order to enable it to produce its important internal secretion.

In certain ordinary dyscrinisms, especially those that have developed in association with a well-defined hypothyroidism, iodine often may be added to the other treatment with distinct advantage. Since, in its molecular composition, the chief thyroid principle is more than two-thirds iodine, thyroid therapy is often advantageously reenforced by some convenient form of iodine, as sodium iodide (from 5 to 10 min. of saturated solution once a day in milk, just before food), Protiodin (a proteinate of iodine, insoluble in water, from which the iodine is gradually liberated as the protein binder is digested in the upper bowel: dose, 2 or 3 tablets t.i.d. with meals), or Lipoiodine—Ciba (1 or 2 tablets daily, well chewed and dissolved in the saliva).

In no thyroid disorder is iodine therapy more beneficial than in the glandular enlargement known as simple goitre (57). Here the administration of thyroid extract may work wonders, but the results are more pronounced if, in addition to the homostimulation expected from the thyroid therapy, something by which the thyroid may be able to make a larger amount and a better quality of its hormone is given simultaneously.

A formula of my own that is built on the principle outlined above is known as Iodized Thyroid Co.* To a usual dose of the standardized double-strength thyroid preparation (24), a suitable iodine salt is added, the iodide of iron being selected for its coincidental hematinic value. The combination is further reenforced with nucleic acid (nuclein), and constitutes an excellent remedy for simple goitre. Many allied disorders, notably those of the ovaries, are equally responsive to its persistent administration. I know of a number of obstetricians who use this formula or something very much like it for several weeks several times during pregnancy, especially in women who develop a slight enlargement of the thyroid during the first few months of pregnancy.

To push this therapy, it will often seem proper to use iodine in other forms. I frequently prescribe Iodex ointment (a piece the size of a large pea) to be rubbed into the goitre itself; or, in cases in which there is an associated dysovarism, to be well worked into the skin over each ovary. The ointment should be applied every night for several weeks.

To prevent simple goitre or to reduce one that is already developing, some iodine salt (such as sodium iodide) may be mixed with the table salt, so that from 1 to 5 gr. is used each day for several weeks, once or twice a year. Iodostarine—Roche, each tablet containing 0.01 Gm. of iodine, is frequently used as a prophylactic in school children, especially girls, and particularly when they live in a goitre area. The prophylactic dose of this product is 5 gr. each day in divided dosage taken in saline or other combinations over a period of from ten days to two weeks, twice a year.

Ten years ago, H. S. Plummer, of the Mayo Clinic, noted that iodine in the form of the standard Lugol's solution (iodine 5 per cent. and potassium iodide 10 per cent. in water, each cubic centimeter containing 1.95 gr. or 126 mg. of iodine) caused temporary improvement in the symptoms of hyperthyroidism. Depending upon the severity of the toxemia, a dose ranging from 1 to 3 cc. a day is given in divided doses, well diluted; this is continued for two weeks or longer. It is surprising that iodine is of value in such opposite thyroid conditions as myxedema and Graves' disease, but it is; and, too, the benefit is more rapid and spectacular in the hyperthyroid cases. Within a day or two after this treatment is initiated, the pulse rate is reduced and with it the basal metabolic rate. Occasionally this may obviate the necessity of surgical intervention, even in most serious cases. The reason for this is not very clear, but, following a series of histological studies, David Marine has suggested that this treatment brings about a temporary change in the structure of the thyroid cells approximating that found in simple colloid goitre, and "that the pressure of this colloid temporarily blocks the absorption of the thyroid secretion."

Usually the Lugol treatment of exophthalmic goitre is a preliminary to necessary surgical intervention, and it is now a standard procedure by means of which the prognosis has been radically improved. But, like surgery itself, this method fails to reach the hidden etiologic factors. In true adenoma of the thyroid the response is by no means so satisfactory as it is in hyperthyroidism, and there is still a difference of opinion as to whether it should be used in such cases. The suggestion has been made that Lugol therapy is so effective in true hyperthyroidism and so unsatisfactory in thyroid adenoma that the beneficial reaction to it is of differential diagnostic value.

104. HEPATOBILIARY ENCOURAGEMENT

MANY OF the chronic diseases are known to have associated with them a more or less serious toxemia—if, indeed, this intoxication is not a prominent part of the etiology of, as well as the predisposition to, the disease itself. The list includes certain dermatoses, drug addiction, epilepsy, hypertension, intestinal stasis, malnutrition, migraine, neurasthenia, nephritis, obesity, rheumatism, and tuberculosis.

In all these conditions, and in several more in the same general class, there is undue stress on every detoxicating mechanism in the body, including the liver. In view of the magnitude of the hepatic detoxicative service, this may be a preponderant factor in many a patient who is not considered as actually suffering from an hepatic disorder. If, as we have seen elsewhere (72), migraine is a manifestation of sensitization to certain proteins that should have been destroyed, surely the same principle may be an essential factor in many other forms of toxemia. Obviously, then, the aggressive encouragement of so important a factor as the detoxicating capacity of the liver will be vitally helpful in every chronic toxemia.

It is freely granted that each disease listed above has an essential etiologic peculiarity that has nothing to do with the liver function, and for which there is another therapy, endocrine or otherwise; nevertheless, this common denominator that we are now discussing is tremendously important. Therapeutic intervention directed at this factor may make real changes in other non-hepatic toxemias such as hypothyroidism, hypoparathyroidism, or demineralization, as well as in the resistance, nutrition, and general elimination.

The gist of the matter is this: In each of these toxic disorders, *consider the liver*. Encourage its biliary activities (by recourse to bile salts); arouse its detoxicative chemistry (by catalysis with the hepatic-detoxicating hormone); wring out the liver (by the time-tried methods). In so doing, you not only will reduce the toxemia that is the outstanding feature in each of the diseases listed here, *but you will be sparing the other endocrine regulators from having to carry on a part of the detoxication that should be done by the liver.*

Surprising, rapid, and extended are the results from such intervention. Remarkable and fundamental is the improvement that follows such treatment. Actually, every endocrine function is improved, and the results of other indicated organotherapy—thyroid, adrenal, pituitary, parathyroid, pancreas, and even gonad—are frequently increased beyond expectation. This is attributed to the intimacy of the relation between the detoxicative duties of every mechanism involved, which includes the entire eliminative machinery.

There follows an outline of a standard routine for the treatment of the liver aspects of practically all chronic diseases, including every one of the conditions named in the foregoing:

1. *Spare the liver* by
   (a) Cutting down on proteins.
   (b) Unloading the toxic bowel.
   (c) Diluting the cellular wastes.
2. *Stir the liver* by
   (a) Calomel—only once, at the start.
   (b) Magnesium sulphate.
   (c) Hot water in the morning; or the alimentary flushing with normal saline solution already referred to (99).
3. *Arouse the secretion of bile* by
   (a) Bile salts.
4. *Stimulate detoxication* by
   (a) Anabolin,* for its anabolic detoxicative hormone influence.
   (b) Thyroid, when there is clear evidence of hypothyroidism.
   (c) Boldine, for its known ureagenetic effect.
   (d) Alkalies, to build up the mineral reserve that is always depleted by the excessive acid wastes in this class of patients, as explained previously (100).
5. *"Remind the liver to behave,"* for the habits of years will soon reassert themselves, and without persistent nudging the liver will almost inevitably slip back to its former apathy.

To enable the reader to translate this outline into a convenient procedure, there is given here a routine that has proved itself to be life-saving times without number:

1. Omit all animal proteins (but not milk) for two or three months, especially the easily putrefiable proteins such as the twice-cooked meats, etc. Stress the value of fruit juices.

2. Calomel (once only), perhaps 2 gr. divided into ten doses, one every fifteen minutes. (Follow with a bottle of citrate of magnesia.) A glass of hot water each morning.

3. Then prescribe Bile Salts Co.,* making the signature read: 1, q.i.d. between meals for three days, double this dose for three days, treble dose for three days (perhaps even quadruple the dose for three days). Continue until free bile appears with the stool, then reduce the dose to 1, q.i.d. Repeat this routine *p.r.n.*, especially in stubborn cases. (An important point must be referred to here: Many preparations containing bile salts are commonly

used as cathartics, and practically all of them contain phenolphthalein, cascara, or other alimentary stimulants. As evacuants these products are undoubtedly useful, but as biliary stimulants the added cathartic interferes with the effects of the bile salts, for it is not possible to give enough of them because by so doing one would be giving too much of the associated cathartic. The idea of bile therapy is to supply the makings of more bile and thus facilitate a corresponding activity on the part of the liver cells. For this reason bile salts should be given alone or associated with liver therapy, and the dosage gradually increased until the liver is producing bile at such a rate that it no longer can be absorbed and used over again—in other words, until there is free bile with the stools.)

4. After two or three weeks of this biliary regulation, or after the bile flow is well started but before using all the bile salts formula, give Anabolin Solution,* 1 cc. intramuscularly daily or every other day for ten or fifteen doses. With this, give Anabolin Tablets, 1, t.i.d. If there is well-defined evidence of hypothyroidism, add thyroid in very small doses—not more than two ½-gr. tablets a day—and continue it for several months.† If acidosis is marked, remineralize for a short time, thus: Calcium Phosphorus Co.* 3 tablets (of 1 Gm.) crushed, with water *one hour before food,* twice a day (*i.e.,* with the early morning hot drink or before dinner) for three weeks; thereafter, on alternate weeks.

5. After three or four weeks of Anabolin therapy as outlined, replace it with Hepato-Splenic Co.*—a combination of Anabolin, spleen substance, and boldine—1 sanitablet q.i.d. at meals and at bedtime. Later, give it every other week or every other fortnight and, if necessary, continue for months and months. This formula is confidently recommended as an excellent means of maintaining the hepatic activities influenced by the treatment outlined here, and is a necessary measure because of the inevitable tendency on the part of the liver to relapse into its old lazy habits.

Perhaps this may seem like a lot of treatment, and at first the response to it may not be an entirely pleasing experience for your patients, but it gets clinical results that it is confidently believed are unattainable in any other way.

†When thyroid therapy is needed, it is better to give small doses for a long time than large doses for a short time. This is reasonable, because such treatment is essentially an attempt to educate the thyroid to do its own work again, and naturally takes some time. The giving of small doses avoids the innumerable misfortunes due to the common overdosage of thyroid, which has disgraced endocrine therapy.

105. SPECIFIC AND NON-SPECIFIC PROTEIN THERAPY

ONE CANNOT get away from the idea that specific protein therapy—against allergy, pollinosis, and the like—brings about its response through the glands of internal secretion. The theory that protein sensitization and its therapy have something to do with the endocrines, is gaining ground. Not least among the suggestive findings is the fact that hereditary endocrinopathies are frequently associated with hereditary tendencies to some variety of protein sensitization, including the placental protein sensitization that causes the vomiting and nausea during the early weeks of pregnancy (84).

Several students interested in both allergy and endocrinology have concluded that in some mysterious fashion the endocrines are involved (36). The clinical picture known as vagotonia (91) often includes a tendency to urticaria and anaphylaxis. The only way to establish this fully is by the collation of a large amount of clinical experience, and this is gradually being done.

I have personally observed that dyscrinism is not unusual in protein sensitive patients. Further, one occasionally finds a person whose sensitiveness varies with his endocrine balance; for example, hay-fever, asthma, or urticaria is sometimes worse immediately before a delayed or abnormal menstruation.

Naturally, this has led to the recommendation, often repeated in these pages, to treat dyscrinism when it is accompanied with various other disorders, in the hope that with the response to the needed endocrine regulation there will be some benefit to the other conditions.

The same thought applies also to non-specific protein therapy. Does the reaction to, say, injections of a colon vaccine or milk protein involve the endocrine glands? Or, to put it another way, are not the symptom-complexes that are known to respond to non-specific protein therapy also frequently associated with endocrine disorders? The answer to this is so obviously in the affirmative that it is not unreasonable to suppose that any beneficial reaction to non-specific protein injections is due partly to an endocrine response.

Another phase of this matter has to do with what has been called "reaction therapy," or the wilful causing of febrile reactions with the expectation of utilizing them to arouse certain physiological responses. For instance, an infection with malaria has been found of real value in the control of so hopeless a disease as paresis, or G.P.I. This is mentioned only by way of illustration, not explanation.

Again, a similar idea is the basis of a new treatment for chorea. Lucy D. Sutton, of New York City, reports having successfully treated twenty-four cases of chorea by fever therapy, the hyperpyrexia having been brought about by injections of typhoid vaccine.

Without a doubt non-specific therapy is combined with the organotherapy in the mass injections of testicular emulsion referred to elsewhere (88). In a number of cases the reactions are such as we find following an injection of milk, and this may give an additional explanation for some of the results reported.

The conclusion drawn from the experiences prompting these remarks is that the study of conditions in which either specific or non-specific protein therapy is of accepted value, should include the evaluation of the endocrine services and the regulation of dyscrinism. On the other hand, an endocrine problem accompanied with protein sensitization is less likely to respond to one kind of needed treatment alone.

Some physicians have put this idea into practice in their treatment of certain types of endocrine dysfunction in which organotherapy has to be continued over long periods, and the response to it leaves something to be desired. Instead of trying to step up the dosage when things are lagging, give one or more injections of 5 cc. of Lactigen (Abbott) or Aolan (Metz) intramuscularly in the hope that, during the response to these proteins, the patient's endocrines also will react and, therefore, that they will become temporarily more sensitive to the proffered hormones. It is a peculiar observation that certain substances may exert seemingly contradictory or paradoxical effects, that they may be stimulants or sedatives according to circumstances; in other words, that they have a tendency to induce disturbed physiological processes to return to normal. J. St. Lorant, of Prague (*Wien. Arch. f. inn. Med.,* Dec. 10, 1924, ix, p. 341), points out that this peculiarity of action is characteristic especially of the sensitization produced by the parenteral introduction of non-specific proteins. It tends to increase physiological processes and to change them in the direction of what is physiological, affecting not only pathological conditions but also constitutional peculiarities that are not quite normal. Under the influence of parenteral protein sensitization, chronic inflammatory processes at first pass through a stage of activation (by way of reaction), after which they show a tendency to healing.

It was Ralph H. Spangler, of Philadelphia, who in 1909 suggested this method. He used rattlesnake virus (crotalin) and, of course, his idea was ridiculed severely. Yet he persisted, and through the years has reported some highly interesting clinical results. Much of his work has been in the treatment of epilepsy. Repeatedly in his later articles he refers to dysfunction of the endocrine glands and to menstrual irregularities in females, which, he reminds us, are frequently encountered in epileptic patients. The adjuvant effect of non-specific protein injections (in his case, crotalin injections)

consists in stimulation of the glandular function and in general plasma activation. Also, by altering the permeability of the cell walls, the oral use of dried extracts of the glands of internal secretion is often enhanced. In a more recent article (*Atlantic Med. Jour.*, Dec., 1924, xxviii, p. 138), Spangler considers "The Non-Specific Protein Reaction as an Adjuvant to Endocrine Therapy," and his conclusions, based upon clinical experience, are as follows:

"1. The non-specific protein reaction has become recognized as a factor in restoring deranged metabolism, and one of its chief values seems destined to be its synergistic action when used as an adjuvant to other therapeutic measures.

"2. The selection of a satisfactory agent to produce non-specific reactions for therapeutic purposes is important. Venom protein (crotalin) solution, prepared in sterilized ampules with accurately measured doses, offers an agent, the practical advantages of which are: a mild local reaction without systemic depression, and a method for regulating the strength of dosage and frequency of administration by differential blood-counts.

"3. The glands of internal secretion are recognized to be regulators of metabolism, but factors which control and influence their activity are not definitely known.

"4. Since the non-specific protein reaction and the glands of internal secretion both influence metabolism and probably immunity, they would logically seem to be synergistic."

John A. Kolmer, of Philadelphia (*Clin. Med. and Surg.*, July, 1931, xxxviii, p. 472), summarizes this matter as follows:

"Non-specific protein therapy is still largely upon an empiric basis. The mechanism is unknown, but the production of fever, along with quantitative and qualitative changes in the leukocytes, with an increase of non-specific bactericidal substances of the blood and of phagocytosis and focal reactions of hyperemia and exudation, are regarded as being of most importance.

"Many agents have been employed, especially typhoid and other vaccines, intravenously, and sterilized milk or milk proteins intramuscularly.

"Severe constitutional reactions from intravenous injections are dangerous in chronic myocarditis, and especially in syphilis.

"Especially good results from non-specific protein therapy have been observed in some cases of chronic recurring iritis, chronic gonococcus infections, infective arthritis, recurring erysipelas, neurosyphilis, etc. It has also been employed with success in the treatment of some acute infections like pneumonia, typhoid fever, septicemia, etc."

It is very difficult to obtain dependable information upon which to pass sound judgment, but the impression has been gained that such injections are definitely helpful in endocrinopathies also.

106. PELVIC DEPLETION

HYPOTHYROIDISM CAUSES cellular infiltration; dysovarism often produces pelvic congestion; certain utero-ovarian disorders and postpartum difficulties bring on a condition of uterine bogginess or subinvolution. There is a suitable and wonderfully effective organotherapy for each of these disorders, but it is good policy also to deplete the pelvis—mechanically.

This can usually be done, promptly and satisfactorily, by tamponade with a hypertonic saline combination. By means of a glycerin-gelatin vaginal suppository (made by the Abbott Laboratories, North Chicago, Ill., List No. 930), containing magnesium sulphate in suitable combination, it is possible to introduce into the upper vagina materials that, when dissolved by the tissue serum, bring about by osmosis a depletion that actually removes much of the congestive fluid in the cervix, uterus, and adnexa. The flow of serum frequently is so great that the patient should be warned to wear a pad.

Half a dozen such local treatments during one or two weeks, will often make the outcome of other treatment very much more satisfactory.

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107. PYRIDIUM IN GONADO-PROSTATIC DISORDERS

SINCE THE perfection of the series of genito-urinary antiseptic dyestuffs of which Pyridium (Merck), Mallophene (P. W. R.), and Serenium (Squibb) are types, I have recommended them a number of times as supplementary therapy in cases needing the specific stimulation that organotherapy offers in impotence and hypogonadism (58), and also in prostatic hypertrophy (85).

If a patient has a latent gonorrheal infection of the posterior urethra or the seminal vesicles, if there is an old *B. coli* infection of the prostate itself, or if there is retention of urine with trigonitis or something worse, a potent urinary antiseptic will be of value. In fact, it should be the rule in every case of hypogonadism to ascertain whether or not such lurking infections are present to interfere with the success of the hormone measures.

It is surprising how active these antiseptics are, it being possible to administer them by mouth in such concentration (0.2 Gm. t.i.d. for ten days or more) that within a day or two the mucosa of the entire urinary tract is impregnated with the dye (and the patient's clothes highly tinted in the meantime!). Even the seminal fluid in the prostate and vesicles is colored.

Before starting therapy in these cases, as with Gonad Co.* or Prostate Co.,* it is especially necessary to be sure that latent genito-urinary infections are uncovered and controlled.

108. PHAGOCYTIC STIMULATION

SINCE MOST of the responses of the organism are reciprocal, we expect the endocrine responses to be closely related to other equally vital physiologic reactions. Thus there are ways and means of reestablishing the endocrine balance other than by the direct influence of organotherapy.

Among recent advances in therapeutic practice are the findings of Burr Ferguson, of Birmingham, Alabama, who through the years has built up a concept of therapy based on the responsiveness of the white blood-cells in various circumstances and a procedure that apparently modifies the phagocytic influences with advantage in many problem cases. Working along lines originally conceived by Metchnikoff, he has materialized a new advance in therapeutics which should interest every endocrinologist.

I am indebted to this writer for the following résumé outlining a method whereby the very ordinary hydrochloric acid is made the agent in bringing about some quite extraordinary clinical responses that have enabled numerous clinicians to get better results from endocrine therapy in many a case:

"Accumulated clinical experiences in the treatment of infections by the use of drugs, resulted in the therapeutic nihilism of the nineties, to be succeeded by the highly fanciful Ehrlich 'side-chain theory,' in which certain hypothetical elements were thought to exert some curative influence, with the blood as the channel. After twenty-five years of effort with millions of clinical determinations, this theory is authoritatively said to have collapsed.

"Apparently, however, some force, factor, or element in our bodies must be credited with bringing about many recoveries that without this factor would have had a lethal ending. Would it not be logical to attribute this successful resistance to the invasion of the body by harmful organisms, to the 'vital spirit' of Hippocrates, though perhaps it might be made a bit more modern by calling it 'the non-specific mechanism'? It must be admitted that neither of these terms is very clear, so a vital spirit is just as easily comprehended as a non-specific mechanism.

"If we name this subtle reaction 'phagocytosis,' there is an immediate clearing of the mental processes, and we find ourselves involved in the consideration of the problems of immunity. It is a demonstrable fact that Nature mobilizes these nomadic blood-cells around and about any injury or point of invasion of harmful micro-organisms, from a reserve of billions which are available in the general circulation. Carrel has demonstrated this excess in the numbers of the white cells in and about wounds, and maintains that their presence and activity are essential elements in the repair of such lesions. That the phagocytes are present in greater number about the margin of wounds cannot be denied, but Carrel's conclusion that these cells are an essential element in healing might be questioned with propriety. However, his conclusion is almost as easily demonstrable clinically, as the statement that white cells mobilize about lesions of the skin. For, if the natural inflammatory

reaction increases the number of white cells about lesions, and one can still further increase the number of the repair force by the injection of almost any drug used for intravenous or intramuscular injection in the treatment of infections—milk, diphtheria antitoxin, Splenocrin, or hydrochloric acid—a change in the speed of the healing process is immediately noticeable, thus confirming the truth of Carrel's conclusion.

"No micro-organism serves better to illustrate the therapeutic value of the artificial stimulation of the white cells than the tubercle bacillus. The polymorphonuclear cell will attack, engulf, and digest any and all hostile organisms that we know, save the tubercle, and some that we do not yet know —the influenza coccus, rod, or spirillæ, for example. This cannot be proved clinically because I have never seen an influenza organism, though I know the evidences of their presence and activity, and that these responses may be quickly controlled by the artificial stimulation of the white cells with so simple a product as a solution of hydrochloric acid. Hence the conclusion is inevitable that the influenza organism must have been found and destroyed. An interesting confirmation is furnished by this failure of Nature to induce any aggressive action against *B. tuberculosis,* which would appear to demonstrate the conclusive proof of the generalization of Metchnikoff that 'the one constant factor in immunity, whether innate or acquired, is phagocytosis.' Now if these cells are capable of being artificially stimulated, this phagocytic phenomenon of the engulfment of the tubercle bacillus by the polynuclear cells, should be evidence of the most conclusive kind. Exactly this happens, and usually an improvement in the condition of the patient is seen within three or four days after beginning the application of this therapeutic idea.

"Most of my observations have followed intravenous injections of a dilution of the U.S.P. acid hydrochloric 1:1500 in distilled water, the usual dose being 10 cc. daily or at longer intervals. This procedure is not, as some have believed, a dangerous one, and usually such an injection causes neither reaction nor discomfort.

"This measure is a means of arousing a vital defense reaction in which the phagocytes play an important part that can be demonstrated by accepted micromethods. I do not believe that this phagocytic response can occur without an associated reaction in the other defenses of the body. In other words, the picture that we see under the microscope is but a part of a far larger beneficial reaction which undoubtedly involves the endocrine organs and their capacity to regulate and correlate the body functions as a whole.

"While much of my work has been done with the previously mentioned hydrochloric acid solution, I have been especially interested in some of the possibilities from the use of certain endocrine products, especially from the spleen. Without a doubt, this organ has an important part in regulating the defenses of the body, but as yet we have not come to the end of knowledge on this matter.

"I have on my desk now two reports of other means of stimulating the white cells in the treatment of tuberculosis. One was sent to me from Groningen, Holland, by the translator, H. A. Bosma. The paper was written

in 1912 by the late Prof. W. J. Van Stockum, of Rotterdam, and reports some remarkable results in the treatment of pulmonary tuberculosis as well as tuberculous infections of the bone, glands, and skin by injection of an irradiated extract from the spleen. Van Stockum says that after the injection of the splenic extract he always found an immediate drop in the white count, followed within a few hours by an increase well above the original count. Further, he noticed the same phenomenon that is now so eagerly looked for by me, and most consistently found, after beginning the series of injections of the hydrochloric acid, *i.e.,* the engulfment of the tubercle bacillus and with it the coincidental improvement of the patient. Van Stockum tried this plan in about 150 cases, when his untimely death stopped further determinations. My attention was called to this forgotten work because Bosma, in Holland, became interested in reports of my intravenous use of hydrochloric acid and wrote a paper in *American Medicine* (1925, N.S., xx, p. 45), explaining the chemical reactions that followed such injections.

"Another reprint is from Gerald B. Webb, of Colorado Springs, who uses the hyperemic method by placing a tourniquet about the upper arm for half an hour, thus stopping the venous return flow, and in this manner bringing about a great increase in the number of white cells in the general circulation and a still further increase when the retarded blood is allowed to go back into the general circulation. It is said that after this procedure the lymphocytes attack and engulf the tubercle. As my own work has been altogether with the polymorphonuclear leukocytes, I can say nothing of this attack by the lymphocytes.

"Since the profession is still without an accepted principle for the treatment of infective disease (see *Jour. Am. Med Assn.,* April 11, 1931, xcvi, p. 1232), the theory of the antibodies and amboceptors of Ehrlich having collapsed, I hope I may have said something that may induce a consideration of the 'vital spirit' of Hippocrates or the phagocytes of Metchnikoff for immediate application in the repair of wounds, the demolition of pathologic tissue, and the elimination of the enemies of our kind—the germs and their poisons."

There is very much more about this subject, for which there is not space here; but the interested reader can study with advantage the following papers by Burr Ferguson:

"Leukocytes in Infection and Immunity; Application of Teaching of Metchnikoff" (*Clin. Med. and Surg.,* Aug., 1927, xxxiv, p. 585).

"The Leukocytes Stimulated by Hydrochloric Acid" (*Clin. Med. and Surg.,* Aug., 1928, xxxv, p. 563).

109. THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

IN THE winter of 1915 I migrated from New York to California. During the period of enforced professional idleness while awaiting a meeting with the Board of Medical Examiners, I took occasion to communicate with a number of colleagues who had shown their interest in the internal secretions by writing for reprints of various articles published on the subject, who had purchased my book, "Practical Hormone Therapy," or who in other ways had made contacts indicating their leanings in the same direction as my own.

A letter was written to all these, asking for their cooperation in materializing an idea given to me in 1913 by my late friend, Eugene Hertoghe, in Antwerp. While on a recent trip to Europe, I had just gone up to Antwerp from Paris where I had been absorbing some very vital points about the endocrines and organotherapy especially. I chanced to speak of a point that had been mentioned to me by Léopold-Lévi, the renowned thyroid specialist in Paris. This happened to be new to Hertoghe, for the idea had never been published. In the course of our conversation, Hertoghe said something like this: "So many things are happening in this field that there ought to be a special society to keep the workers in the subject in touch with what is going on elsewhere in this line."

This fermenting thought would not down, so quite early in 1916 I started the correspondence mentioned above. Mimeographed letters were sent out to interested colleagues and the result was the founding of a society which was formally organized in Detroit in May, 1916, under the name of "The Association for the Study of the Internal Secretions." Its official bulletin is *Endocrinology,* the first issue of which was prepared by me late in 1916 and issued under date of January, 1917.

Now that this subject has come into its own, The Association for the Study of the Internal Secretions is more widely appreciated to-day than in those early years, and its annual meeting (usually held in connection with the meeting of the American Medical Association) is a get-together that is always appreciated by those fortunate enough to be able to attend.

The Honorary Secretary is Dr. F. M. Pottenger, 1930 Wilshire Blvd., Los Angeles, California. Annual membership dues of $6.00 include the subscription to the Association's bimonthly journal, *Endocrinology.*

It is a pleasure to recall the early effort to "sell this idea" and to see how successful this effort has been.

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110. THE ENDOCRINE LIBRARY

THE AUTHOR'S attempt throughout this book has been to express the consensus about a given subject rather than a discussion of the available literature. Such discussions inevitably would be lengthy, for there is so very much in print on almost every facet of each subject.

Occasionally there appears in the literature an idea that originally had an element of individuality in it—for instance, the notion that compensatory enlargement explains simple prostatic hypertrophies, the pluriglandular basis of most menopausal disorders, the thyroid function test, or the hypothesis of hormone hunger. Naturally, I feel a tinge of pride each time such an idea receives the approval of first one writer and then another.

The endocrine literature is already far too cumbersome and hopeless from the practical standpoint of the practitioner of medicine. No one is in a better position to appreciate this than those connected with the Harrower Endocrine Library (920 East Broadway, Glendale, California). In fact, all who visit this institution readily admit that it is the most complete and useful library of endocrine material that they have ever seen. Here we have a staff of workers who find themselves fully occupied in keeping us in touch with the literature on endocrinology. As a result of their efforts during the years, there are in this library more than 1700 books on the internal secretions and matters directly pertaining thereto, and more than 60,000 clippings, abstracts, reprints, and pamphlets—all catalogued and cross-indexed. There are 250,000 cross-index and author cards. Nearly one thousand items, taken from between 250 and 300 publications, go through the library *each month*—representing a tremendous amount of work.

The reader may have remarked on the absence of numerous bibliographies throughout this book. Of course clinical evidence and certain statements are properly credited, but an attempt at a complete acknowledgement is altogether out of the question. Indeed, many a criticism of the leading endocrine books and papers is that the attempt to give credit where credit is due is literally ponderous.

Remember that Biedl's monumental work includes 480 pages of references! Remember that most of a 879-page volume of the five-volume set by Barker, Hoskins, and Mosenthal is a list of references that has long since been incomplete in view of the thousand or more items that have been added to the subject each month since this work was published nine years ago.

In order to make this book as complete and valuable as possible, it was thought advisable to include a list of the principal endocrine books and monographs. Naturally, the list is incomplete, for of necessity it must be limited;

and, too, by the time it is in print perhaps a dozen new ones will have appeared. Obviously, it is biased for we record only those that we have in our library and we lean to those in our own language, despite the fact that more than half (582) of our one thousand books on strictly endocrine subjects are not in the English language.

Then, too, as we are human, undoubtedly some excellent and practical works have been overlooked and hence are not listed here. But here follows a list of the makings of a very sizeable and useful endocrine library:

A LIST OF ENDOCRINE BOOKS

ENGLISH

Endocrinology

BANDLER, S. W.: The Endocrines. Philadelphia: W. B. Saunders Co. 1920. Pp. 486. $7.

BARKER, LEWELLYS F., *et al.*: Endocrinology and Metabolism. New York: D. Appleton and Co. 1922. Five Volumes. Pp. 4770. $48.50.

BERKELEY, W. N.: The Principles and Practice of Endocrine Medicine. Philadelphia: Lea and Febiger. 1926. Pp. 368. $4.50.

BERMAN, LOUIS: The Glands Regulating Personality. New York: The Macmillan Co. 1921. Pp. 300. $3.50.

BIEDL, ARTUR: The Internal Secretory Organs. London: John Bale, Sons and Danielsson, Ltd. 1912. Pp. 586. 45/–.

BROWN, W. LANGDON: The Endocrines in General Medicine. London: Constable and Co., Ltd. 1927. Pp. 144. 6/3.

CANNON, WALTER B.: Bodily Changes in Pain, Hunger, Fear, and Rage. New York: D. Appleton and Co. 1915. Pp. 311. $3.

COBB, IVO GEIKIE: The Organs of Internal Secretion. London: Baillière, Tindall and Cox. 1921. Third Edition. Pp. 311. $3.

COBB, IVO GEIKIE: The Glands of Destiny. London: William Heinemann. 1927. Pp. 290. 7/6.

CROFTON, W. M.: An Outline of Endocrinology. Edinburgh: E. and S. Livingstone. 1929. Pp. 163. 6/–.

CURSCHMANN, HANS: Endocrine Disorders. London: Oxford University Press. 1929. Pp. 188. $4.

DERCUM, F. X.: The Biology of the Internal Secretions. Philadelphia: W. B. Saunders Co. 1924. Pp. 241. $2.75.

DICKSON, I. W.: Rational Gland Therapy for Women. London: H. K. Lewis and Co. 1926. Pp. 96. 4/6.

ENGELBACH, WM.: The Principles and Practice of Endocrine Medicine. Springfield, Ill.: Charles C. Thomas. 1931. Four Volumes. Pp. 1800. $35.

FALTA, W., and MEYERS, M. K.: Endocrine Diseases. Philadelphia: P. Blakiston's Son and Co. 1923. Third Edition. Pp. 669. $8.50.

GLEY, E.: The Internal Secretions. New York: Paul B. Hoeber. 1917. Pp. 241. $2.

LIPSCHUTZ, A.: The Internal Secretion of the Sex Glands. Baltimore: Williams and Wilkins Co. 1924. Pp. 513. $6.

SAJOUS, CHARLES E. DE M.: Internal Secretions and Principles of Medicine. Philadelphia: F. A. Davis Co. 1922. Tenth Edition. Two Volumes. Pp. 1853. $15.

VINCENT, SWALE: Internal Secretions and the Ductless Glands. London: Edward Arnold and Co. 1924. Third Edition. Pp. 463. $10.

Adrenals

GOLDZIEHER, MAX A.: The Adrenals: Their Physiology, Pathology, and Diseases. New York: The Macmillan Co. 1929. Pp. 436. $7.50.

Gonads

BELL, W. BLAIR: The Sex Complex. London: Baillière, Tindall and Cox. 1916. Pp. 233.

FORSDIKE, SIDNEY: Sterility in Women: Diagnosis and Treatment. New York: William Wood and Co. 1929. Pp. 133. $3.50.

FRANK, ROBERT T.: The Female Sex Hormone. Springfield, Ill.: Charles C. Thomas. Pp. 321. $5.50.

GIBBONS, ROBERT A.: Sterility in Women. London: J. and A. Churchill. 1923. Pp. 244. 12/6.

GILES, ARTHUR E.: Sterility in Women. London: Henry Frowde. 1919. Pp. 227. $3.

LEVENTIS, C.: Sex Glands Function and the Human Life. Detroit: C. Leventis. 1930. Pp. 132. $2.

LYDSTON, G. FRANK: Impotence and Sterility. Chicago: The Riverton Press. 1917. Pp. 333. $4.

PARKES, A. S.: The Internal Secretions of the Ovary. New York: Longmans, Green and Co. 1929. Pp. 242. $7.50.

VECKI, VICTOR G.: Sexual Impotence. Philadelphia: W. B. Saunders Co. 1920. Sixth Edition, Revised. Pp. 424. $3.

Pancreas

JOSLIN, ELLIOTT P.: The Treatment of Diabetes Mellitus. Philadelphia: Lea and Febiger. 1928. Pp. 998. $9.

LABBE, MARCEL: A Clinical Treatise on Diabetes Mellitus. London: William Heinemann. 1922. Pp. 382. 18/–.

MACLEOD, J. J. R.: Carbohydrate Metabolism and Insulin. New York: Longmans, Green and Co. 1926. Pp. 357. $6.

MACLEOD, J. J. R., and BANTING, F. G.: The Antidiabetic Functions of the Pancreas and the Successful Isolation of the Antidiabetic Hormone, Insulin. St. Louis: C. V. Mosby Company. 1924. Pp. 69. $1.50.

MACLEOD, J. J. R., and CAMPBELL, W. R.: Insulin. Baltimore: Williams and Wilkins Co. 1925. Pp. 242. $4.

Pituitary

BELL, W. BLAIR: The Pituitary. London: Baillière, Tindall and Cox. 1919. Pp. 348. $8.

CUSHING, HARVEY: The Pituitary Body and Its Disorders. Philadelphia: J. B. Lippincott Company. 1912. Pp. 341. $5.

Thyroid

BRAM, ISRAEL: Exophthalmic Goiter and Its Nonsurgical Treatment. St. Louis: C. V. Mosby Company. 1920. Pp. 438. $5.50.

BRAM, ISRAEL: Goiter Prevention and Thyroid Protection. Philadelphia: F. A. Davis Co. 1928. Pp. 327. $4.

CRAMER, W.: Fever, Heat Regulation, Climate, and the Thyroid-Adrenal Apparatus. New York: Longmans, Green and Co. 1928. Pp. 153. $6.

CRILE, GEORGE W.: The Thyroid Gland. Philadelphia: W. B. Saunders Co. 1922. Second Edition. Pp. 297. $5.

CROTTI, ANDRE: Thyroid and Thymus. Philadelphia: Lea and Febiger. 1922. Pp. 774. $12.75.

DANISH

KRABBE, KNUD H.: Histologiske undersögelser over corpus pineale. Copenhagen: Jul. Gjellerups. 1915. Paper. Pp. 107. Kr. 5.15.

FRENCH

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CARNOT, PAUL, *et al.*: Les progrès récents en thérapie endocrinienne. Paris: J. B. Baillière et fils. 1927. Paper. Pp. 293. Fr. 24.

CHOAY, E.: Des extraits opothérapiques. Paris: Vigot Frères. 1911. Paper. Pp. 176.

GLEY, E.: Les grands problèmes de l'endocrinologie. Paris: J. B. Baillière et fils. 1926. Paper. Pp. 178. Fr. 15.

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LAEMMER, MARCEL: Opothérapie clinique. Paris: Masson et cie. 1925. Paper. Pp. 151. Fr. 10.

LAROCHE, GUY: Opothérapie endocrinienne. Paris: Masson et cie. 1925. Paper. Pp. 256. Fr. 12.

LEGRAND, RENE: Le système endocrino-sympathique du Vieillard. Lille: O. Marquant. 1926. Paper. Pp. 172. Fr. 20.

LEMATTE, L.: L'opothérapie du praticien. Paris: A. Maloine et fils. 1923. Paper. Pp. 239. Fr. 5.

LEOPOLD-LEVI: Opothérapie endocrinienne. Paris: Livre de France. 1922. Paper. Pp. 160. Fr. 3.50.

LUCIEN, M., *et al.*: Traite d'endocrinologie. Paris: Gaston Doin. 1925, 1927, 1929. Paper. Three Volumes. Pp. 1971. Fr. 100.

MOINSON, LOUIS: La thérapeutique par les glandes (opothérapie). Paris: Le François. 1928. Paper. Pp. 168. Fr. 8.

NOBECOURT, P.: Les syndromes endocriniens dans l'enfance et la jeunesse. Paris: Ernest Flammarion. 1923. Paper. Pp. 314. Fr. 10.

PARHON, C. I., and GOLDSTEIN, M.: Traité d'endocrinologie. Jassy: Viata Romineasca. 1923. Paper. Pp. 467. Lei 352.

PARISOT, J., and RICHARD, G.: Les glandes endocrines: leur valeur fonctionnelle. Paris: Gaston Doin. 1923. Paper. Pp. 247. Fr. 5.

PERRIN, MAURICE, and HANNS, ALFRED: Les sécrétions internes. Leur influence sur le sang. Paris: J. B. Baillière et fils. 1923. Paper. Pp. 280. Fr. 12.

PORAK, R.: Les syndromes endocrines. Paris: Gaston Doin. 1929. Pp. 554. Paper. Fr. 28.

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GALLAIS, ALFRED: Le syndrome génito-surrénal. Paris: Vigot Frères. 1914. Paper. Pp. 424.

LUCIEN, M., and PARISOT, J.: Glandes surrénales et organes chromaffines. Paris: F. Gittler. 1904. Cloth. Pp. 79.

PORAK, R.: Les glandes surrénales et l'hypophyse. Paris: Gaston Doin. 1922. Paper. Pp. 110. Fr. 7.

SERGENT, EMILE: Etudes cliniques sur l'insuffisance surrénale. Paris: A. Maloine et fils. 1920. Second Edition. Paper. Pp. 423.

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ARON, MAX: Vie et reproduction. Paris: Masson et cie. 1929. Paper. Pp. 366. Fr. 38.

BARBAUD, CH., and LEFEVRE, CH.: La Puberté chez la femme. Paris: A. Maloine et fils. 1897. Pp. 282. Fr. 12.

CHAMPY, CH.: Sexualité et hormones. Paris: Gaston Doin. 1924. Paper. Pp. 376. Fr. 30.

DARTIGUES, L.: Le renouvellement de l'organisme. Paris: Gaston Doin. 1929. Paper. Pp. 424. Fr. 60.

RETTERER, ED.: Puberté et maturité sexuelle. Paris: Gaston Doin. 1925. Paper. Pp. 208. Fr. 10.

Pancreas

AUBERTIN, EMILE: L'insuline. Paris: Gaston Doin. 1926. Paper. Pp. 490. Fr. 45.

CHOAY, ANDRE: La sécrétion interne du pancréas et l'insuline. Paris: Masson et cie. 1926. Paper. Pp. 570. Fr. 65.

Parathyroids

MOREL, LOUIS: Les parathyroïdes. Paris: A. Hermann et fils. 1912. Cloth. Pp. 344. Fr. 40.

Pituitary

CHAUVET, S.: L'infantilisme hypophysaire. Paris: A. Maloine et fils. 1914. Paper. Pp. 333. Fr. 10.

PENAU, H., *et al.:* L'hypophyse. Paris: Les Presses Universitaires de France. 1929. Board. Pp. 249. Fr. 45.

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BERARD, LEON: Corps thyroïde: Myxœdèmes, thyroïdites, et strumites. Goitres: Cancers thyroïdiens. Paris: J. B. Baillière et fils. 1921. Paper. Pp. 308. Fr. 7.

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